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INTERDEPENDENCE OF FUNCTION IN ANESTHESIA

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In words like those of John Dewey, it may be said that functions require the cooperation of organism and environment. Breathing is an affair of the air as truly as of the lungs. The same air that under certain conditions ruffles the pool or wrecks buildings under other conditions purifies the blood and conveys thought. The outcome depends on what air acts on. Function, then, may be regarded as the manner of employing and incorporating the environment. The nature of the surroundings will therefore be bound to have its say. We are subject to ambient influences. Physiologically, it is a fatuity to give precedence to any one vital function or native faculty over another. Each is essential to life. As Edmund Burke has put it, "When we define, we seem in danger of circumscribing nature within the bounds of our own notions, which we often take up by hazard, or embrace on trust, or from out of a limited and partial consideration of the object before us, instead of extending our ideas to take in all that nature comprehends, according to her manner of combining."

And yet it is not altogether inexcusable, teleologically, to give some priority to the functions residing in the blood, which, as Cowdry [1] says, circulates actively as a life-giving, integrating and regulating medium. The regularly circulating blood not only welds the countless numbers of cells into an individual, because it enables all of them to feed at the same table—at the places occupied by their forefathers—and to breathe the same air, but also integrates their activities in many other ways. By providing an efficient medium of intercourse between the cells it has made possible specialization in cellular performances, so that the secretions of the cells of the pituitary for example, passing first into the tissue fluid and seeping through the capillary walls into the blood stream, can influence all the other cells of the body. As cells acquire the ability to do better and better, less and less like individuals in a community, they become dependent more and more on their fellows specialized in other directions. Without the interchanging powers of the blood this dependency on other far distant cells would not be possible.

Thus even to the darksome grove and secret penetralia of the cerebral cortex, where resides the highest of all functions, namely thought, the body fluids are circulated so that metabolism may take place—even here where are centered those intricate contingencies that knit our lives and those potencies which are coordinated into energy. It is here that in general anesthesia the desired reversible effects take place, so that it would seem, in the language of William James, that the accidental fences which the individual builds are broken and the mind is plunged into the continuum of cosmic consciousness. Although the selective action in general anesthesia is referable to the brain and although there are many theories extant on the mechanism of this action, it is still an open question. Of the whole diadem of hypotheses, that which has to do with the oxidation processes in the brain, the close association between these and cerebral activity, is perhaps the most feasible. Quastel [2] points out that the gray matter of the brain has a high rate of oxygen consumption and a continuous supply of blood to the brain is essential for the normal functioning of this organ. From six to eight seconds of interruption of cerebral circulation produces loss of consciousness. Herein is a signally definitive instance of interdependence of function: neither the nervous system nor its immediate external environment, the blood stream, could function alone. Without nervous regulation (Cowdry) of muscle the blood would not flow, and without arterial blood the nervous system would soon die. The closest cooperation prevails. The blood stream supplies the cells with the necessities of life, including special stimulating or inhibiting substances contributed by their neighbors, and removes the waste. The nervous system controls the rapid integration of bodily functions by means of nerve impulses. As Gerard [3] says, "This universal capacity of protoplasm to hand on excitation is developed into an exquisite talent by the nerve cells. Along their fantastically extended straight processes the nerve impulses, propagated excitation waves, rush to various destinations." Quastel has suggested that an anesthetic is adsorbed from the blood at a specific area or center of the nervous system. Here it hinders the cells of the nervous center from oxidizing pyruvic acid, lactic acid and dextrose. The peculiar effects of anesthetics will depend on the characteristics of adsorption in various parts of the nervous system. It has been shown by Jowett [4] that a definite inhibition of respiration is produced by anesthetic concentrations sufficient to produce deep narcosis. He states that inhibition of dextrose oxidation may be the cause of anesthesia. Quastel intimates further that anesthetics bring about a local hypoxia in those parts of the nervous system in which they are adsorbed,

Read before the Section on Anesthesiology at the Ninety-Third Annual Session of the American Medical Association, Atlantic City, N. J., June 11, 1942.

1. Cowdry, E. V.: A Textbook of Histology, Philadelphia, Lea & Febiger, 1934.

2. Quastel, J. H.: Respiration in the Central Nervous System, Physiol. Rev. **19**: 135-183 (April) 1939.

3. Gerard, R. W.: Higher Levels of Integration, Science **95**: 309-313 (March 27) 1942.

4. Jowett, M.: The Action of Narcotics on Brain Respiration, J. Physiol. **93**: 322-335 (April 14) 1938.

despite the presence of oxygen, by virtue of interference with the oxidation of dextrose at a given nervous center. It is not irrelevant to recount the findings of Sellei and Mayer;[5] in effect, respiration is decreased in the cerebral cortex of rats after ether, chloroform and ethyl chloride. These agents do not influence the thalamus or the white matter. Contrarily, evipal soluble decreased respiration of white matter and thalamus but did not affect that of the cerebral cortex.

Thus may be illustrated the influence of anesthetics on function in the central nervous system when these are in solution in the blood. But the functions of the circulating blood may themselves be disturbed in anesthesia. A striking example is seen in high spinal anesthesia when breathing is depressed, when the heart is slowed, when the blood pressure falls and when there is blood dilution; in other words, when the circulation becomes sluggish and the oxygen-carrying power of the blood is reduced. Then, in the light of interdependence of function, the central nervous system will be robbed in part of its most important substrate, dextrose, and, as well, be deprived of its proper supply of oxygen, both so vitally important for purposes of internal respiration. The brain demands at least a minimum concentration of dextrose and a constant supply of oxygen.

With regard to external respiration, Gesell[6] draws attention to the fact that rapid adjustments in the exchange of carbon dioxide for oxygen depend on pulmonary ventilation and the circulation of the blood. These two systems function in harmony under similar influences at and from the respiratory and the circulatory centers and their outlying chemoceptors. By themselves, the chemical mechanisms, central and peripheral, are capable of acting efficiently. Complementary control obtains through the physical forces of stretchings of the carotid sinus, the aortic arch and the proprioceptive endings in the lungs. Whether caused by hypoxia or hypercapnia, hyperpnea signifies impaired oxidation or increased H ion concentration, or both, at the chemosensitive structures. There is evidently a very finely adjusted interaction. However, the part played by reflex factors in influencing pulmonary ventilation has been demonstrated by Harrison[7] on anesthetized animals in which hyperpnea occurred when a limb was moved passively, even though the blood was intercepted and the leg was connected with the body only by the sciatic nerve. When the sciatic nerve was cut, movements of the leg no longer affected breathing even though vascular communications were reestablished. How pervadingly interwoven and abundant is function between the nervous system, the circulation and respiration. To consider any one without the others is to be blind and halting.

On account of the regard that anesthetists have always had for the functions of the liver and the kidney, something may be said of their interpenetration. The superfluity of structure in these organs, the reserve of power they possess and the integration of their activities through the blood stream, through nerve influences and hormone essences, are so bewildering and so extensive that I can do no more at this time than to exemplify a little. Despite disparate structure, functions are correlated in action whether they are acquired with seemingly reasoned purpose or are innate, spontaneous and altogether inconscient. Recently Van Slyke[8] has followed some of the paths in the body that are taken by amino acids after digestion and absorption in the alimentary tract. Among other things, he says that "one could watch the work of the liver in taking up the amino acids and destroying them, turning their nitrogenous parts into urea for excretion by the kidneys. Unreasonable and wasteful though it seems, a large part of the amino acids absorbed from the intestine appears to be captured and destroyed by the liver and never to have a chance to reach and nourish the other tissues." It is interesting parenthetically to posit beside this statement one by Carlson:[9] "The normal kidneys are very effective regulators of the composition of the internal environment, the blood, but fail to eliminate excess thyroxin, excess parathyroid hormone, excess pituitary growth hormone, and also excess insulin. Is this a failure in evolution? Or are we just on the way?" According to Van Slyke, it would appear that every protein molecule in the living body is itself alive in the sense that it is continually changing and renewing its structure through the continual replacement of amino acids. The detoxifying effects of the amino acids have been known for some time and we are now all familiar with Quick's[10] hippuric acid test for liver function. Incidentally, it is not inappropriate to say that anesthetists ought to know the liver function tests so clearly set forth by Mateer and his associates.[11] It may be worth while pointing out that the liver transforms amino acids into dextrose;[12] that this organ stores protein against the occasion of starvation or hemorrhage;[13] that the Russian chemists Braunstein and Kritzmann,[14] have shown that the amino acids can be constructed from ammonia and keto acids; that, by transmethylation from methionine, the essentials choline and creatine are made in the body;[15] that the sulfur-containing amino acids cystine and methionine protect the liver from intoxication by chloroform;[16] that when the reserve tissue proteins are depleted by fasting and the plasma proteins are depleted by bleeding[17] the proteins can be rapidly restored in tissues and plasma by intravenous amino acid administration, which might be suitable at times when feeding by mouth is impossible or inadvisable, and that, by condensation, by oxidation-reduction reactions and in more profound ways,* the amino acids "can serve as source material for certain vitamins, hormones and other compounds with physiological function still to be identified."

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6. Gesell, R.: Respiration and Its Adjustments, in Luck, J. M., and Hall, V. E.: Annual Review of Physiology, Stanford University, Calif., Annual Reviews, Inc., 1939, vol. 1, pp. 185-216.

7. Harrison, T. R.: Failure of the Circulation, Baltimore, Williams & Wilkins Company, 1939.

8. Van Slyke, D. D.: Physiology of the Amino Acids, Science **95**: 259-263 (March 13) 1942.

9. Carlson, J.: Man's Body and Man's Behaviour, Sigma Xi Quart. **29**: 170-181, 1941.

10. Quick, A. J.: Clinical Value of the Test for Hippuric Acid in Cases of Disease of the Liver, Arch. Int. Med. **57**: 544-556 (March) 1936.

11. Mateer, J. G.; Baltz, J. L.; Marion, D. F.; Hollands, R. A., and Yagle, E. M.: A Comparative Evaluation of the Newer Liver Function Tests, Am. J. Digest. Dis. **9**: 13-29 (Jan.) 1942.

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13. Rubscheit-Robbins, Frieda S., and Whipple, G. H.: Reserve Store of Hemoglobin Producing Substances in Growing Dogs as Influenced by Diet, Am. J. Physiol. **112**: 27-32 (May) 1935.

14. Cited by Braunstein, A. E., and Azarkh, R. M.: Trans-Amination of *l*- and *d*- Amino Acids in Normal Muscle and Malignant Tumors, Nature, London **144**: 669-670 (Oct. 14) 1939.

15. du Vigneaud, Vincent; Cohn, M.; Chandler, J. P.; Schenck, J. H., and Simmonds, S.: Utilization of Methyl Group of Methionine in Biological Synthesis of Choline and Creatine, J. Biol. Chem. **140**: 625-641, 1941.

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17. Madden, S. C.; Noehren, W. A.; Waraich, G. S., and Whipple, G. H.: Blood Plasma Protein Production as Influenced by Amino Acids: Cystine Emerges as Key Amino Acid Under Fixed Conditions, J. Exper. Med. **69**: 721-738 (May) 1939.

Furthermore, I know of no better instance of effort toward interdependence of function than that which occurs in the acidosis of anesthesia when phosphoric acid leaves the muscles, travels through the blood and sojourns in the liver until such time as kidney function is reestablished, during recovery, when it is partly redistributed and partly excreted.[18]

With all these interdependent chemicophysiologic links before one, and other unimaginable, superabundant and infinite co-adaptations of functioned tissue, correlated delicately in a raveled web, there comes to the non-Philistine mind a consideration of the disturbances which may occur on account of anesthesia, particularly now, in circumstances of war, when there are so many shocked patients whose conditions demand immediate surgical intervention and in whom that Gordian knot of the physician in wartime, the vicious circle of shock, has all too often to be dealt with. It becomes a matter of particular importance, therefore, continually to bear in mind what is known of the conduct of shock and what is known of the effects of the drugs used in anesthesia. To illustrate, let me draw attention to some of the actions of ether: how it causes a sharp reduction in the volume of the blood and a relatively large increase in the interstitial fluid,[19] how it causes the blood solids to increase by 2 to 3.5 per cent of the total weight of the blood while the individual tends to become poikilothermic,[20] how it produces an immediate depression of function in the liver [21] and kidney,[22] and how it invariably precipitates a true acidosis.[23] Surely these are enough to suggest that ether ought not to be given to a patient in shock during which fluid is leaking into the tissue spaces to such an extent that blood volume may be so dangerously lowered as to deprive the blood vessels of sufficient fluid for circulation. The administration of ether will undoubtedly increase the breakdown in the interdependence of function seen in shock.

With regard to hypoxia, the respiratory depressant action of many anesthetics is thought to be, at least in part, due to a reduction in sensitivity of the respiratory center. It is not unlikely that when in shock the respiratory center is already suffering from anoxia and any one of many narcotic drugs may lead to its earlier failure. Substances which reduce the effective ventilation may harm the shocked patient, since the reduction in ventilation of itself will tend to increase the existing tissue hypoxia from which the whole organism is being affected. It is clearly undesirable to allow further disturbance of the metabolism from an increase in oxygen want, when the individual may have already passed the nadir of depression.

While this is not a discourse on shock, it is not altogether inapposite to say that the "local" and "block" forms of regional anesthesia seem to be especially suitable for cases of shock and that, no matter what the method of anesthesia, one is well advised regularly and actively to give oxygen throughout the administration.

One might go on interminably, even to that interdependence of function seen in the dead parts of our beings, such as the body fluids, including the great fluid fractions of lymph and blood, which like the wood walls and tubes of the higher plants are highly serviceable to the organism.

Finally, for all interpenetration of function, some simile may be seen in the words of George Santayana: "Mind owes its origin, growth, and development to matter, but the strange child repays his parent a hundredfold with the riches he pours in her lap. Nature gives birth to consciousness: consciousness gives value to nature."

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ABSTRACT OF DISCUSSION

DR. RALPH M. WATERS, Madison, Wis.: I gather that what Dr. Bourne has been saying is that the effects of administration of an anesthetic agent cannot be tabulated as simple stimulation of one function and depression of another but that, in addition, there is likely to be a secondary effect on a second function caused by the stimulation or depression of the first and not necessarily caused directly by the anesthetic drug. As a common example, if the agent per se causes a depression of respiratory exchange there will result a depletion of the oxygen content of the blood. This hypoxia in turn will put an extra strain on the heart in an attempt to bring about an increase in cardiac output. If the heart is lacking in adequate reserve strength, circulatory failure may follow. The unhappy result in such a case would not be a direct effect of the anesthetic agent per se but rather it would furnish evidence of the reciprocal relationship and interdependence of the two functions of respiration and circulation. Dr. Bourne has called to our attention many such relationships and he has by no means exhausted the instances of interdependence. There is scarcely a single function of the body that, when modified by anesthesia, fails in its modified condition to have an effect on other physiologic mechanisms. To simplify the teaching of the pharmacologic effects of anesthetic drugs, I have been guilty—along with others—of trying to make a table listing the agents and, in columns following them, the various organs or functions of the body. Under each organ or function was placed the characteristic effect of each drug. The result was anything but fortunate. To correlate the contents of the table with observations made during the administration of an anesthetic was often difficult or impossible. We must continue to observe and record, watch closely what we see of functional change during anesthesia, write down our impressions at the time, familiarize ourselves with the evidence from the laboratories as it appears in the literature and hope that, by keeping everlastingly alert, we may improve our understanding of functional disturbances caused by anesthetic drugs directly, and of the secondary changes in other functions resulting from the interrelationships which Dr. Bourne has indicated.

DR. RALPH M. TOVELL, Hartford, Conn.: It is with profit that we have listened to Dr. Bourne's presentation of the circuitous and interwoven relationships of human physiologic functions. The need for further research to unravel the interrelationships of function has been amply demonstrated. He has succeeded admirably in showing that an anesthetist's thought patterns during administration of an anesthetic should not be limited to either respiratory function or circulatory function but should encompass the body as a single working unit. He stated the crux of the problem when he said "How pervadingly interwoven and abundant is function between the nervous system, the circulation and respiration. To consider any one without the others is to be blind and halting." We as clinicians can second Dr. Bourne's implied appeal for continuance of unremitting effort in research. Those of us without laboratory facilities are duty bound to have within our ken the information that has already been proved to be factual.

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21. Rosenthal, S. M., and Bourne, Wesley: The Effect of Anesthetics on Hepatic Function, J. A. M. A. **90**: 377-379 (Feb. 4) 1928.
22. Stehle, R. L., and Bourne, Wesley: The Effects of Morphine and Ether on the Function of the Kidneys, Arch. Int. Med. **42**: 248-255 (Aug.) 1928.
23. Bourne, Wesley, and Stehle, R. L.: The Excretion of Phosphoric Acid During Anesthesia, J. A. M. A. **83**: 117-118 (July 12) 1924. Stehle and Bourne.[9]

POSTDIPHTHERITIC LARYNGEAL STENOSIS

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LOS ANGELES

Obstructions of the larynx herein considered are those which are brought about by changes in the intralaryngeal tissue or the supporting framework. These are essentially chronic and are the sequelae or end results of some acute inflammation or injury.

While the term laryngeal stenosis is used, actually the site of obstruction is most often subglottic and frequently extends for a variable distance into the upper part of the trachea. Stenoses of this type are almost invariably in the region of the conus elasticus, which has for its upper limit the vocal cords and extends down through the subglottic region to become blended with the lining of the upper part of the trachea. In this region there is areolar tissue surrounding the conus elasticus, which is more abundant in young children than in older persons. Swelling of this tissue is easily provoked by inflammation and trauma, thereby causing acute obstruction of the airway. This occurs in inverse

TABLE 1.—*The Etiology of Laryngeal Stenosis*

1. Following acute infections:
(a) Diphtheria
(b) Pyogenic infections such as tracheolaryngitis
2. Trauma
(a) Contusions and fractures of the larynx
(b) Gunshot wounds
(c) Cut throat
(d) Escharotics
3. Healing processes following:
Typhoid, typhus, tuberculosis, syphilis and scleroma
4. Following surgical procedures
High tracheotomy—laryngofissure fulguration

ratio to the age of the patient. When this area is involved in inflammatory reaction, regardless of the cause, it is particularly intolerant of instrumentation. Thus violent reactions occur which are out of all proportion to the apparently trivial trauma following the passage of bronchoscopic tubes in young children with preexisting laryngitis. Reactions such as these are seen particularly in children under 2 years of age, and tracheotomy is often necessary to prevent suffocation. If intubation is preformed a reaction such as is encountered in bronchoscopy will occur, but as long as the tube remains in situ it will forcibly maintain open passage. However, if for any reason the tube is taken out or is extruded before the reaction subsides, there will be a tendency for the lumen of the larynx rapidly to become obstructed.

Obstructions due to acute laryngeal inflammation may disappear spontaneously, or there may be subsequent tissue changes that will ultimately lead to chronic stenosis. These tissue changes are persistent swelling and hypertrophy of the subglottic tissue, necrosis and granulation tissue proliferation and the production of cicatricial tissue. These three processes may be present singly or in varying combinations. The laryngeal framework may also be involved, which adds to the gravity of the situation.

Read before the Section on Laryngology, Otology and Rhinology at the Ninety-Third Annual Session of the American Medical Association, Atlantic City, N. J., June 11, 1942.

CAUSE

By far the most common cause of laryngeal stenosis is diphtheria.

This report is concerned mainly with the group of patients with laryngeal stenosis in the contagious service of the Los Angeles General Hospital during the last twenty-two years, a group which was under my supervision during this time (1920-1942).

According to the records of the Los Angeles County Board of Health, there were 40,107 cases of diphtheria diagnosed during the period from 1920-1942; 10,402 of these were treated in the general hospital, 1,744 of which were cases of laryngeal diphtheria. In this group there were 448 deaths; 1,296 patients survived and were discharged from the contagious ward. Of the survivors, 108 were referred to the laryngologic department for treatment of laryngeal obstruction. The patients of this group ranged in age from 13 months to 3½ years, the average age being under 2 years. The obstruction in all these cases was mainly below the true cords; that is, in the subglottic area involving the region of the conus elasticus. Ninety of this group of 108 patients were wearing tracheotomy tubes and the remaining 18 were breathing through the larynx with varying degrees of difficulty. Eleven patients with tracheotomy tubes also had minor degrees of obstruction. In the 2 latter groups of 29 patients persistent subglottic swelling was treated by galvanocautery puncture. All these patients recovered in a few weeks or months. The remaining 79 patients, all wearing tracheotomy tubes, had varying degrees of severe laryngeal obstruction. In these patients the lumen was obstructed by granulations and there was necrosis of the soft tissue. As healing progressed the tendency to scar tissue formation became increasingly more evident.

At weekly intervals the lumen was tested by closing the tracheotomy tube with a finger. Instrumentation was limited to direct laryngeal examination and the passing of a laryngeal sound to test the size of the lumen. The retrograde sounds of Lynah were found particularly useful. Exuberant granulations were partially removed. If the tonsils and adenoids were infected, their removal was advised. Dilating rubber sections were not inserted until the healing process was fairly well advanced.

It is during the healing stage of such cases that utmost judgment in treatment must be exercised. In this phase there is an optimum amount of treatment that should be effected in order to produce satisfactory results. If this optimum is exceeded by overstrenuous dilation or excessive traumatization to the already inflamed structures, one runs the risk of augmenting the condition. On the other hand, if dilation therapy is not started at this stage or soon after the patient is almost certain to end up with a grossly stenosed or obstructed larynx. Obviously, therefore, the technic in successfully handling these cases centers around an accurate estimation of the condition of the larynx and its toleration to subsequent treatment. In any case which does not fit into a treatment category it is probably best to proceed very cautiously with minimal dilation at first in order to remain under the threshold of the secondary reaction due to overintensive therapy.

Notwithstanding our best efforts, 28 of this group ultimately had complete stenosis and required a tracheo-

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laryngostomy operation. Four of the 108 patients died during the course of active treatment: 1 with intercurrent disease, 1 from suffocation when his tracheotomy tube came out at home, 1 from lung and brain abscess and 1 with pneumonia.

Treatment of laryngeal stenosis has for its objective the establishment of a permanent and adequate airway

Fig. 1.—Rubber section ready to be drawn into the larynx.

through the larynx. This is accomplished by protracted treatment with some dilating device which is introduced into the larynx.

Of all the various dilating devices thus used, soft rubber in the form of tubing or coremolds has been found most satisfactory. Soft rubber is well tolerated by the laryngeal tissue and also has the property of increasing slightly in size while in the larynx, thus exerting continuous gentle but firm pressure.

In order to be satisfactory, treatment must be accomplished with a minimum of injury. Since patients in this category are small children, especial care must be exercised to prevent psychic trauma. This calls for some method whereby these treatments can be carried out with a minimum of pain and discomfort.

The method here described was devised for the introduction of rubber sections into the larynx through a small tracheal stoma or through a tracheotomy wound.

Rubber sections are made from urethral catheters size 20 to 30 French. They are cut about 2½ inches long, are beveled at both ends on an emery wheel and are marked with their size with silver nitrate.

The introducer is made from a rubber urethral catheter. The dilated end with about 8 inches of the catheter is used. A metal stylet is inserted into the lumen filling all but 2 inches of the flared end. To the cut end of the tube is fastened a metal cap or ferrule that has a smooth conicle end. The stylet is bent so that the curve of the catheter describes an arc of a 6 inch radius. It is an easy matter to introduce this device through the tracheotomy wound; as it appears in the mouth it is grasped, and the section which has previously been placed in the flared end is drawn into the larynx. Holding the section in situ with a forcep through the tracheotomy wound, the introducer is completely withdrawn from the mouth, leaving the laryngeal section in the larynx.

PRELIMINARY PREPARATION OF THE SECTION

The length of the section is determined by calculating the distance from the upper part of the cricoid to the upper margin of the tracheotomy wound. After a proper length has once been found it is used as a guide in preparing future sections. The lower end of the section is cut on a slant with scissors so as to fit the curve of the tracheotomy tube. A silkworm gut suture on a needle is passed through the anterior wall of the section and tied, the ends being left free to be attached to the tracheotomy tube. After the section has been placed in the larynx the sutures emerge from the tracheotomy wound. These are threaded onto the tracheotomy tube before it is inserted. The tracheotomy tube is a standard one which has been modified by having a breathing opening placed in the greater curvature; just anterior to this opening is a small metal loop. The free suture ends, having been passed through this loop one from each side, are tightened as the tracheotomy tube slips into place, thus anchoring the section and tube into one unit. The sutures are finally brought through small holes in the guard where they are tied.

The period of time these rubber sections are left in place is important. If they are changed too frequently there is added trauma to the tissues and epithelization of the passage is retarded. If left too long, they become foul and contribute to the inflammation. Calcareous salts become encrusted on the tube in six weeks. The best results were found by changing the section every three weeks.

Most of the patients with incomplete stenosis were able to dispense with treatment at the end of twelve months. Several were cured in a much shorter period, the shortest time being three months. Four patients are still under treatment after five years. In cases of cicatricial stenosis, the period of active treatment exceeded eighteen months. After this the patients were kept under continued observation. Recurring stenosis was treated by a short period of dilation with rubber

Fig. 2.—Rubber section in place; note compression of the anterior wall of the section by constricting scar tissue.

sections. These children have developed quite normally. The tracheal opening was covered with a patch of adhesive and permanent closure was deferred until further growth of the larynx, which in more than half of the severe cases was not until the age of puberty. An increase in the size of the larynx by growth of the supporting framework is an important factor for a

good ultimate result. All these children have audible voices, although rather rough and low pitched. Those in this group who continued with minor degrees of laryngeal obstruction had adequate airways after the age of puberty. Only 1 patient of this group is still wearing a tracheotomy tube after puberty.

There is a decided decrease in the incidence of diphtheria in Los Angeles County, as shown in table 2, compiled from the records of the board of health and the general hospital.

Virulence of diphtheria infections has also shown a decided decrease. The percentage of laryngeal involvement has decreased two thirds.

In the five year period 1922-1927, of all diphtheria patients in the contagious pavilion 15.2 per cent had laryngeal infection. In the period 1937-1942 this had decreased to 5.4 per cent. The last cicatricial stenosis in this service occurred in 1936, and since that date there have been referred only 5 other cases, all presenting minor degrees of laryngeal obstruction.

TABLE 2.—*Diphtheria (Nose and Throat) in Los Angeles County, January 1920-January 1942*

Fiscal Year	Total in Los Angeles County	Total in Los Angeles General Hospital	Total Laryngeal Diphtheritic in Los Angeles General Hospital	Total Deaths in Los Angeles General Hospital	Total Laryngeal Deaths in Los Angeles General Hospital
1920	2,557	205	Not classified	15	Not classified
1921	3,602	276	Not classified	26	Not classified
1922	2,265	1,075	175	142	52
1923	3,777				
1924	4,393	756	137	125	36
1925	2,342	508	73	69	22
1926	3,119	373	66	48	15
1927	2,853	650	151	100	31
1928	2,037	612	137	97	33
1929	1,512	984	91	47	15
1930	1,304	725	96	72	25
1931	1,787	541	63	64	21
1932	2,602	917	184	137	39
1933	1,435	781	113	100	25
1934	1,201	709	86	74	15
1935	905	588	39	55	16
1936	735	451	85	71	24
1937	592	540	87	64	24
1938	741	449	63	52	14
1939	409	435	55	41	12
1940	189	215	22	27	8
1941	215	161	18	29	10
	40,107	10,402	1,744	1,444	448

Population of Los Angeles county: (Figures furnished by Los Angeles Chamber of Commerce)	1920	936,455
	1930	2,302,310
	1940	2,785,643

Postdiphtheritic stenosis is rarely seen in private practice. During this time I saw only 3 such cases which were treated outside of the hospital. The diphtheria staff of the Los Angeles County Board of Health feels that most severe laryngeal diphtheritic infections in young children cause death unless the children are given institutional treatment.

The Los Angeles General Hospital is the only institution in the county that treats contagious diseases. The 10,402 diphtheria patients treated in this hospital during the period 1920-1942 constituted about one fourth of all cases of diphtheria occurring in the entire county. All patients with resultant laryngeal stenosis from this group were referred to the eye and ear hospital for treatment, which was carried out under my supervision.

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ABSTRACT OF DISCUSSION

DR. FLETCHER D. WOODWARD, Charlottesville, Va.: Los Angeles County is to be congratulated on a very active campaign of immunization, since these cases have dropped from a maximum of 4,000 a year to a maximum of around 180 to 200 in the past few years. In my experience I have felt that the use of the intubation tube has played some role in the creation of stenosis. I still advocate intubation, and I believe that it is the method of choice in the treatment of laryngeal diphtheria. I have made it a rule that, if there is any difficulty as a result of using the intubation tube, tracheotomy should be done. I think that this procedure will reduce the incidence of stenosis. As to treatment, Dr. Jesberg had an ingenious method and a successful method, as his statistics will prove. I have not used this method, but I expect to employ it in 2 or 3 cases which I have under my care at this time. I have been using the dilators of Jackson, and I have recently used the dilators of Dr. Broyles, but these only dilate at the time one is using them, and one does not get the effect of the continuous pressure of rubber in this area. I have used the rubber tube for other types of stenosis after the method of Schmieglow, and I believe that rubber is the answer to many of these problems.

DR. M. F. ARBUCKLE, St. Louis: Most of us do not have an opportunity to see as much material as the author has had. There are two or three points that I should like to call attention to, with regard to etiology. He mentioned the virility of the organism and intubation. Ill fitting intubation tubes, of course, traumatize the larynx, which is already infected. When one uses an ill fitting intubation tube one is certain to have a tracheotomy, and it is usually a hurry-up one. Nobody can do one in a hurry as well as one can do it when one has time to set it up. I was astonished when I read Schmieglow's Semon lecture on cicatricial stenosis. I was astonished with the ease of mind, apparently, with which he opened and reopened the larynx, when he wanted to work in it, without apparent injury or arrested development. It is true that the lumen of the larynx grows as the child develops. In these cases in which the lumen is closed, it is, of course, not possible to pull up a prosthesis from below or to put it down from above. In those I like to open the larynx and implant the rubber prosthesis and sew the larynx together practically over it. That is where judgment is required not to get pressure too great or too little. I have not seen any of these cases since I entered military service but I heard of one man in whose neck I implanted a rather large rubber tube six months or a year before I left home for an almost complete stenosis due to a razor cut. He had finally reached the point that, by wearing the rubber tube, he had a lumen wide enough so that he could get along without the tube. I am sure absorption takes place from the constant pressure. I would be interested to know, at some other time, the results any of you have had, if you would communicate with me personally, with the use of skin grafts intratracheally, in the effort to prevent adhesions and deformity.

DR. SIMON JESBERG, Los Angeles: When I started this paper I had in mind cicatricial stenosis from all causes, but as I progressed I saw that that would be much too voluminous a paper to present in such a meeting, so I stuck to the diphtheritic; but this same method of introducing the rubber sections is very useful in cases of fractures of the larynx after reduction in which one wishes to hold the larynx in place; or, in a cut throat with cut trachea, they can be introduced through a low tracheotomy wound, holding the trachea in proper alinement until healing takes place. The matter of dilating the larynx of young children is a simple thing, and one can get a lumen large enough in a short time; but it will not remain patent. One must wait until the laryngeal framework supports that lumen, so there is a period in children extending sometimes over many years until that growth occurs. The high tracheotomy is included in the paper as one of the common causes. Another cause that I am running across occasionally is chondritis and collapse of the larynx following laryngeal fissure operation, in which this same method is used after complete healing has occurred.

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THE EXCRETION OF NICOTINE IN BREAST MILK AND URINE FROM CIGARET SMOKING

ITS EFFECT ON LACTATION AND THE NURSLING

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The rapid and somewhat startling increase in the consumption of cigarets in the United States by both males and females during the past decade (1931, 113,500,000,000; 1941, 189,769,000,000) has caused many investigations to determine whether cigaret smoking is harmful. Reports of these investigations are, for the most part, conflicting, making it extremely difficult for physicians to evaluate properly the evidence and to advise their patients on the use of cigarets in disease and in other conditions. Particularly is this true with regard to cigaret smoking by pregnant and parturient women, for the effects of nicotine on the fetus and the newborn infant must be seriously considered. No definite scientific evidence of the effect of cigaret smoking on the human fetus is available. Recently, however, Schoenbeck [1] in an interesting experiment with rabbits showed that exposing pregnant rabbits to the smoke of 1 cigaret a day resulted in litters that had a birth weight approximately 17 per cent less than those of the control litters. The stillbirth rate was ten times as great and the mortality rate was definitely increased, since only one third as many offspring of mothers exposed to smoke were alive at maturity.

A study of the effect of cigaret smoking by parturient women on lactation and on the nursling has been made by many—again with conflicting results. Thompson,[2] from a review of the literature and from personal observation, believes that smoking in moderation probably is a minor factor in influencing lactation. He has not observed, however, a patient averaging 8 or more cigarets daily whose lactation was adequate at three months after delivery.

Hatcher and Crosby [3] noted in a primipara aged 25 who smoked 20 to 25 cigarets daily that the secretion of milk, while abundant at first, rapidly decreased, so that a sample of milk was collected with difficulty after 7 cigarets had been smoked within two hours. They found experimentally that large doses of nicotine suppress the secretion of milk in the cat and cow for longer periods than the time required for the elimination of the greater part of the poison from the body.

Mgalobeli [4] noted that in women employed in tobacco factories there occurred a decided decrease in the number of pregnancies and an increase in the frequency of miscarriages and infant deaths, all of which he attributed to the direct and indirect effects of nicotine on the sex organs. On the other hand, Chiasson [5] found exceptional fertility and lactation in a group of French families the women of which were habitual and constant pipe smokers. H. C. Williamson, H. S. McCandlish, and Ogden Conkey, all of the department of obstetrics of Cornell University Medical College, informed Hatcher and Crosby that they never observed any diminution in the secretion of milk or any effects on a child which could be attributed to the smoking of cigarets by the mother.

Perhaps one of the best investigations on this subject was made by Emanuel [6] in a study of nicotine in the milk of 10 women following the smoking of tobacco. He found that after smoking cigarets nicotine passes in slight amounts into the milk and in much larger amounts into the urine. The nicotine could, at times, be demonstrated one to two hours after smoking, but the main excretion appeared four to five hours after smoking, and in some cases it was still demonstrable seven to eight hours after smoking. The largest amounts of nicotine appeared in the milk when the tobacco smoke was inhaled. A study of the infants when they were fed this nicotine-containing milk revealed that the feces remained unchanged. In 1 child, however, the consistency of the feces changed somewhat, but no general effect occurred. The feces of another child, whose mother was made to smoke 20 cigarets within four hours, became abnormal following the ingestion of the nicotine-containing milk. Smoking cigarets did not influence the quantity of milk produced. This was in disagreement with Sokolov, who found that lactation was inhibited by nicotine. It seemed to Emanuel rather striking that, with the exception of a questionable effect on the intestine, observed in 2 cases, no changes were observed in the infants following the ingestion of nicotine-containing milk. It was questionable whether the amounts of nicotine contained in the milk could be considered toxic doses. He stated that, according to Erben, the lethal dose of nicotine for an adult is 50 mg. and that Schroff demonstrated on himself that the first toxic symptoms appear after the intake of 1 to 4 mg. of nicotine. Since these studies had shown that a maximum of 0.03 mg. of nicotine per liter of woman's milk was found after the smoking of 7 to 15 cigarets, the infant would have to ingest an entire liter of this milk to take up but 0.03 mg. of nicotine, which is an amount below the toxic threshold. The practical conclusion drawn by Emanuel from these observations was that the physician might permit a lactating mother to smoke 5 to 6 cigarets a day, since this amount could not produce any injurious effect on the infant. Any excessive smoking must be prohibited, since following the smoking of more than the 15 cigarets the amount of nicotine passing into the milk may have an injurious effect on the child.

Since the average nicotine content of the American blend type of cigaret is 2.5 per cent,[7] the difficulties of detecting and accurately estimating the minute quantities of nicotine secreted in the breast milk and urine after a variable number of cigarets have been smoked become

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apparent. For the standard colorimetric and chemical tests, large quantities of milk and urine are required, and if the amounts of nicotine are very small they may escape detection. Hatcher and Crosby [8] used the frog for a bio-assay of nicotine in their investigations. This method, somewhat modified, was also used by Thompson in his analysis of milk for nicotine. The frog method for nicotine estimation is a very delicate, qualitative test but gives only a rough quantitative estimate. In Emanuel's study leech segments were used to demonstrate the presence of nicotine in milk and urine by means of Fuhner's method.

In our study, small, transparent, fresh water crustaceans, Daphnia magna, belonging to the Cladocera, were used. Their well developed muscular, nervous and internal organ systems make direct observation of them under normal conditions and under the influence of various drugs extremely easy. Hence they are ideal for the bioassay of various substances. They have already been used to assay strychnine,[9] aphrodisiacs,[9] vitamin E,[10] digitalis [11] and many other drugs.[12]

The propagation of Daphnia has been reported by Viehoever [13] and the methods of standardization have been given by Viehoever and Cohen.[9] Cultured under uniform conditions, Daphnia magna exhibits a definite rhythm and periodicity of growth. In the series of experiments to be described, Daphnia was grown in 0.75 per cent to 0.1 per cent infusion of cow manure (bovung). This method of culture was chosen in preference to other methods because it yielded animals with greater amounts of pigmentation, which facilitated their observation in milk. Reproduction is chiefly through diploid parthenogenesis, hence numerous offspring of genetic uniformity are thus assured.

It was found that Daphnia is extremely sensitive to minute amounts of nicotine, although its effects vary with the age and sex of the animal. In low concentrations younger animals are more sensitive than the older ones. The males are more sensitive than the females. An increase in temperature from 15.5 C. to 32.2 C. also increases the sensitivity. Below 15.5 C. these crustaceans are sluggish: above 32.2 C. they become debilitated. It is thereforefore important to perform experiments at an optimum temperature of 21.1 to 26.6 C. and to have all crustaceans of the same age and sex. Only 10 day old female crustaceans were used in this study. At this age they can readily be differentiated from the males, the females being twice as large as the males and less rapid swimmers.

Under the effects of various known concentrations of nicotine, the reactions of Daphnia were carefully studied so that they could be used as standards for comparative purposes. In concentrations of 1:100,000 and above the primary reaction is a period of paralysis —the time of onset being shorter the greater the concentration. In concentrations above 1:1,000 death quickly follows the stage of paralysis. Between nicotine concentrations of 1:100,000 and below alternate periods of convulsions and paralyses are seen—the convulsions dominating the picture. With decreasing concentration of the drug, the time required for the onset of the reactions becomes longer and less and less severe; so that at 1:2,000,000 periods of relative normalcy may occur. At concentrations of 1:10,000,000 and below the reactions are vague, ill defined and at most only suggestive of a nicotine effect. The term convulsion is applied to disorganized swimming movements of a twirling "loop the loop" type in a vertical plane. It is not a milk or urine effect. These movements were so characteristic of an early effect of nicotine that they were used as a criterion for the presence of nicotine in the milk and urine specimens. After the stage of paralysis and convulsions, swimming on the back occurs. Loop the loop movements have been observed also as an effect of other drugs, notably strychnine. With this drug these movements occur as part of the advanced symptoms and not, as with nicotine, as an early effect.

METHOD OF INVESTIGATION

Fifty-five white primiparas and multiparas between 18 and 36 years of age who were addicted to cigaret smoking were chosen after they had agreed to cooperate in this study. To be eligible, they had to have an apparently adequate supply of milk for their babies.

The lactating mothers were divided into three groups, according to the number of cigarets smoked over a twelve hour period (7 a. m. to 7 p. m.) Group A consisted of occasional smokers (that is, women who smoked 1 to 4 cigarets), group B of moderate smokers (5 to 10 cigarets) and group C of heavy smokers (11 to 20 or more cigarets).

Each mother was permitted to choose her own brand of cigaret, which in all cases was an American blend type. They were instructed to smoke completely each cigaret and, when possible, to inhale the smoke or at least blow it through their nostrils. This was advised to insure the absorption of nicotine. As a rule, the moderate and heavy smokers inhaled regularly, the light smokers less often.

Every effort was made to maintain an adequate supply of milk for the infants by a regular nursing schedule and, when necessary, by expressing the milk with an electric breast pump. After a sufficient quantity of milk was obtained by or for the infants, the residual milk in the breast was expressed and pooled over the twelve hour observation period. It was separated, however, into morning (7 a. m. to 1 p. m.) and afternoon (1 to 7 p. m.) specimens and kept refrigerated until tested for nicotine. The urine to be examined also was collected over this period, pooled, separated into morning and afternoon specimens and refrigerated until tested.

No mother in this study received any medication during the experimental period.

Practically all the mothers started to smoke within two days after their confinement. The specimens of milk for nicotine determination were obtained between the fourth and the ninth day post partum. Determinations could not be made on every specimen because the quantity of milk was insufficient for the tests. Determinations were not made on any specimen of milk or urine more than ten days old. The nicotine concentration was not affected by storage, for specimens of milk and urine known to be nicotine free to which definite amounts of nicotine were added gave accurate estimations after storage for two weeks.

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PREPARATION OF THE MILK

The following method was used to decrease the turbidity and density of the milk so that the Daphnia crustaceans could be more easily observed.

Twenty-five cc. of milk of each specimen was centrifuged for ten minutes to separate the fat. A pipet with a capillary tip was passed through the fat layer and the defatted milk drawn off. This milk was then recentrifuged for one hour to separate some of the proteins and solids as well as the remaining small amounts of fat. The milk was drawn off again, as described, and the residue discarded. Oxygenation of the milk was then effected by bubbling air through it until a foam formed. This was necessary to provide a well aerated medium for the crustaceans. Nicotine determinations, on specimens of breast milk containing known amounts of nicotine and prepared in this manner, showed that nicotine was not lost by such treatment. Difficulty in observing Daphnia was infrequent. When it occurred, observation was facilitated by projecting a light through the milk specimen or by increasing the number of crustaceons in it.

PREPARATION OF THE URINE

The urine was filtered and a 1:10 dilution was made with the culture medium. This was the minimum dilution that was found from experiments to produce no effect on the animals during the period of time required for the estimation of the nicotine content. Undiluted normal urine exerted a toxic effect on the animals within five minutes and a lethal effect on them within twenty minutes.

ESTIMATION OF NICOTINE CONTENT

Fresh solutions of nicotine[14] in Daphnia culture medium, ranging from 1:1,000,000 to 1:10,000,000 concentration for each estimation, were made from a stock solution of 1 per cent nicotine in distilled water. It was found that a stock solution of this strength did not lose any of its potency over a period of two months. No stock solution was used that was older. Ten of the crustaceans were placed in 50 cc. clear glass jars, one jar for each of 2 prepared milk specimens and one jar for each of 5 preliminary control nicotine solutions. These were 1:10,000,000 (0.00001 per cent), 1:4,000,000 (0.000025 per cent), 1:2,000,000 (0.00005 per cent), 3:4,000,000 (0.000075 per cent) and 1:1,000,000 (0.0001 per cent). The small amount of culture medium which was transferred with the animals was removed with fine pipets, care being taken not to injure the animals. With the aid of assistants, and as quickly as possible, the milk specimens and each nicotine control solution were poured simultaneously into the jars.

Careful and continuous observations of the crustaceans in the milk and in the control solutions were recorded for the first five to seven minutes, a stop watch being used to record the time of the reactions. It is during the first five to seven minutes that the most striking nicotine effects can be seen and the time of their occurrence recorded most accurately.

Further observation of the crustaceans was continued, however, for fifteen to thirty minutes in order to record any unusual or latent effects of the nicotine. As the concentration of nicotine in the milk specimen did not always cause the same reactions in the animals as did the concentration of nicotine in a control solution, only an approximate reading at first was obtained. The experiment was then repeated with other control solutions that gave, as near as possible, identical reactions. The specimens of milk that produced identical reactions in the animals as did a known control solution was considered to contain the same concentration of nicotine as the control.

The intensity of the reactions of the animals in the milk could not, however, be compared with those in the nicotine solutions, for it was found that, because of its density, the milk slightly impeded the movements of the animals. For this reason the time factor in these reactions was considered of utmost importance.

The amount of nicotine present in the specimen of urine was determined in a similar manner. The results were multiplied by 10 to correct for the dilution of the urine in preparing the specimen.

RESULTS

Nicotine was found present in every specimen of milk and urine obtained from mothers who smoked cigarets. It was never found in any specimen obtained from mothers who did not smoke. While it would have been of great value and interest to determine the total concentration of nicotine in a twenty-four hour specimen of milk, this was not done because the mothers would not permit their infants to be deprived of the milk necessary for this estimation. The estimations that were obtained, however, permit of significant deductions although it must be remembered that any bioassay cannot be compared to the accuracy of a chemical determination. A definite correlation between the number of cigarets smoked and the quantity of nicotine secreted in the milk and urine was found (table 1.).

TABLE 1.—*Average Concentration of Nicotine in Breast Milk and Urine (Milligrams per Liter)*

	Milk				Urine			
	A. M.		P. M.		A. M.		P. M.	
	Number of Specimens	Average Concentration of Nicotine	Number of Specimens	Average Concentration of Nicotine	Number of Specimens	Average Concentration of Nicotine	Number of Specimens	Average Concentration of Nicotine
Occasional smokers (1-4 cigarets)	6	0.116	5	0.16	7	1.857	6	2.75
Moderate smokers (5-10 cigarets)	27	0.225	23	0.278	32	2.828	31	3.645
Heavy smokers (11-20+ cigarets)	11	0.445	11	0.5	10	4.9	8	6.62

In the group of occasional smokers (1 to 4 cigarets), the average concentration of nicotine in 6 specimens of milk obtained in the morning period was 0.116 mg. per liter and the average in 5 specimens obtained in the afternoon period was 0.16 mg. per liter. In this group the average concentration of nicotine in 7 specimens of urine obtained in the morning period was 1.857 mg. per liter and the average in 6 specimens obtained in the afternoon period was 2.75 mg. per liter.

In the group of moderate smokers (5 to 10 cigarets) the average concentration of nicotine in 27 specimens of milk obtained in the morning period was 0.225 mg. per liter and the average of 23 specimens obtained in the afternoon period was 0.278 mg. per liter. In this group the average concentration of nicotine in 32 specimens of urine obtained in the morning period was 2.828 mg. per liter and the average in 31 specimens of urine obtained in the afternoon period was 3.645 mg. per liter.

14. Nicotine was obtained from the Eastman Kodak Company, Rochester, N. Y.

TABLE 2.—*Data on Fifty-Five Nurslings and Their Mothers Who Smoked Cigarets*

Case	Age of Mother, Years	Number of Years Mother Smoked	Number of Cigarets Smoked, A. M.	Mg. Nicotine per Liter of Milk, A. M.	Mg. Nicotine per Liter of Urine, A. M.	Number of Cigarets Smoked, P. M.	Mg. Nicotine per Liter of Milk, P. M.	Mg. Nicotine per Liter of Urine, P. M.	Number of Cigarets Smoked, 12 Hr. Period	Birth Weight	Weight at Time of Discharge	Net Gain	Net Loss	Days in Hospital	Vomiting and Regurgitation	Average No. of Bowel Movements per Day	Comment
Occasional Smokers (1-4 Cigarets)																	
1	25	7	1	0.1	4	2	0.4	1	3	7 lb. 12 oz.	8 lb. 1 oz.	5 oz.	.....	9	Severe first 3 days, occasionally 8-9 day	4	
2	20	9	1	0.1	..	2	0.1	..	3	7 lb.	7 lb. 4 oz.	4 oz.	.....	10	Occasionally first 4 days	3	Complementary feedings
3	25	9	1	...	2	3	...	4	3	7 lb. 6 oz.	7 lb. 13 oz.	7 oz.	.....	9	Occasionally first 4 days	4	
4	28	10	1	0.1	1	2	...	..	3	5 lb. 12 oz.	5 lb. 12 oz.	.....	.....	10	Occasionally 1-3-6 day	2	
5	26	5	2	0.2	2	2	0.1*	4	4	7 lb. 14 oz.	7 lb. 12 oz.	.....	2 oz.	10	Occasionally 1-2-4-7 day	3	Complementary feedings
6	28	7	1	...	1.5	2	...	3	3	6 lb. 8 oz.	6 lb. 9 oz.	1 oz.	.....	9	Occasionally first 5 days	4	
7	26	1	2	0.1	1	2	0.3*	2	4	6 lb. 8 oz.	6 lb. 6 oz.	.....	2 oz.	10	Occasionally first 6 days	3	
8	22	4	1	0.1	1.5	3	0.1	2.5	4	6 lb. 6 oz.	6 lb. 12 oz.	7 oz.	.....	10	Occasionally first 3 days	4	
Moderate Smokers (5-10 Cigarets)																	
9	22	8	2	0.1	1	3	0.2	5	5	6 lb. 9 oz.	6 lb. 14 oz.	5 oz.	.....	10	Occasionally first 5 days and 8-9-10 day	3	
10	21	6	3	0.2	2	2	0.1*	2.5	5	4 lb.	5 lb. 15 oz.	1 lb. 15 oz.	.....	10	Occasionally first 6 days	3	Premature infant
11	25	7	4	0.1	1.5	1	0.1*	1*	5	6 lb. 5 oz.	6 lb. 12 oz.	7 oz.	.....	10	Occasionally first 9 days	3	
12	28	7	2	0.2	4	3	0.2	2	5	7 lb. 3 oz.	7 lb. 4 oz.	1 oz.	.....	10	Occasionally first 3 days and 7-8-9 day	3	
13	25	8	3	...	1*	2	...	2	5	6 lb. 12 oz.	6 lb. 14 oz.	2 oz.	.....	10	Occasionally first 2 days	3	Complementary feedings
14	28	8	3	...	1*	2	..	1.5	5	6 lb. 9½ oz.	7 lb. ½ oz.	8 oz.	.....	9	Occasionally 2-4-5-6-7-9 day	3	Complementary feedings
15	26	5	2	...	1	3	...	2	5	6 lb. 8 oz.	6 lb. 9 oz.	1 oz.	.....	13	Occasionally 1-2-6-7-11-12-13 day	3	Complementary feedings
16	24	5	2	0.2	2	3	...	4	5	6 lb. 1 oz.	6 lb. 7 oz.	6 oz.	.....	10	Occasionally first 5 days and 8-9 day	3	
17	31	6	3	0.1	2	3	0.1	2	6	10 lb. 3 oz.	10 lb. 2½ oz.	.....	½ oz.	9	None	2	
18	21	8	3	0.1	2	3	0.2	3	6	6 lb. 5 oz.	6 lb. 6 oz.	1 oz.	.....	10	Occasionally 2-5-4 day	2	
19	31	8	3	0.1*	2	3	0.1	1*	6	6 lb. 10 oz.	6 lb. 11 oz.	1 oz.	.....	9	Occasionally 2-3-4-7-8 day	2	
20	30	10	3	...	1*	3	...	2	6	6 lb. 7½ oz.	6 lb. 13 oz.	5½ oz.	.....	10	Occasionally 1-2-3 day	3	Complementary feedings
21	32	8	3	0.1	3	3	†	5	6	5 lb. 13 oz.	5 lb. 14 oz.	1 oz.	.....	10	Occasionally first 9 days	4	
22	28	12	3	0.4	1	3	0.2	..	6	7 lb. 6 oz.	7 lb. 13 oz.	7 oz.	.....	10	Occasionally 1-2-4-5-6-9 day	3	
23	29	12	3	0.1	3	3	0.1	2	6	7 lb. 11 oz.	8 lb. 2 oz.	7 oz.	.....	10	Occasionally every day	3	
24	33	8	3	0.1	1.5	4	0.2	1.5	7	4 lb. 12 oz.	5 lb. 12 oz.	16 oz.	.....	10	Occasionally first 6 days and 8-9 day	3	
25	21	8	3	0.2	2	4	0.35	4	7	6 lb. 4 oz.	6 lb. 8 oz.	4 oz.	.....	11	Occasionally 1-4-5 day	4	
26	27	10	4	...	..	3	...	..	7	5 lb.	5 lb. 10 oz.	10 oz.	.....	10	Occasionally 1-2-6-8-9 day	2	Complementary feedings
27	30	10	3	0.1	2	4	...	4	7	6 lb. 13 oz.	6 lb. 12½ oz.	.....	½ oz.	10	Occasionally 2-3-4-5-6-7-8 day	3	
28	24	7	3	0.2	2	5	0.2	4	8	6 lb. 7 oz.	6 lb. 10 oz.	3 oz.	.....	10	Occasionally every day	2	
29	28	8	3	0.4	5	5	0.4	9	8	6 lb. 2 oz.	6 lb. 6 oz.	4 oz.	.....	9	Occasionally 1-2-4 day	3	
30	21	10	4	0.4	5	4	0.1	3	8	6 lb. 10 oz.	7 lb. 8 oz.	14 oz.	.....	9	Occasionally 1-2-3-4-7 day	3	
31	28	9	3	0.3	3	5	0.4	5	8	6 lb. 13 oz.	6 lb. 15 oz.	2 oz.	.....	10	Occasionally for 9 days	4	
32	27	8	2	...	2	6	...	5	8	6 lb. 9½ oz.	6 lb. 15 oz.	5½ oz.	.....	10	Occasionally first 6 days	4	Complementary feedings
33	22	12	3	0.3	7.5	5	0.2	6.5	8	7 lb. 4 oz.	7 lb. 6 oz.	2 oz.	.....	10	Occasionally 3-4-5 day	3	
34	37	12	4	0.15	1	4	0.3	4	8	7 lb. 11 oz.	7 lb. 5 oz.	.....	6 oz.	10	Occasionally 1-2-5-6-8-9 day	3	
35	25	14	4	0.5	..	4	0.85	..	8	6 lb. 15 oz.	7 lb. 9 oz.	10 oz.	.....	9	Occasionally first 8 days	4	
36	27	8	3	...	4	6	...	4	9	8 lb. 14 oz.	9 lb.	2 oz.	.....	10	Occasionally first 5 days	3	Complementary feedings
37	27	1	3	0.1	..	6	0.4	..	9	7 lb. 9 oz.	7 lb. 4 oz.	.....	5 oz.	8	Occasionally first 2 days	4	
38	25	10	5	0.4	5	5	0.7	5	10	8 lb.	8 lb. 3 oz.	3 oz.	.....	10	Occasionally first 9 days	3	
39	28	5	7	0.4	7	3	0.3	4	10	8 lb.	7 lb. 8 oz.	.....	6 oz.	9	Occasionally first 5 days	3	
40	26	10	3	0.2	2	7	0.4	5	10	7 lb. 14 oz.	8 lb. 6 oz.	8 oz.	.....	11	Occasionally first 4 days	3	
41	21	5	7	0.5	6	3	0.2	5	10	8 lb. 1 oz.	8 lb. 4 oz.	3 oz.	.....	11	Occasionally first 3 days	3	
42	27	10	4	...	3	6	...	5	10	8 lb. 1 oz.	7 lb. 15 oz.	.....	2 oz.	10	Occasionally first 5 days	3	Complementary feedings
43	26	5	4	0.2	5	6	...	4	10	6 lb. 2 oz.	7 lb. 2 oz.	16 oz.	.....	11	Occasionally first 10 days	3	
Heavy Smokers (11-20 Cigarets)																	
44	18	2	6	0.3	4	5	0.2	..	11	6 lb. 7½ oz.	7 lb. 1 oz.	9½ oz.	.....	12	Occasionally first 4 days	4	
45	23	4	4	0.4	6	7	0.5	7	11	7 lb.	7 lb. 11 oz.	11 oz.	.....	10	Occasionally 1-8-9 day	3	
46	21	5	5	0.2	1	7	0.3	5	12	7 lb. 7 oz.	7 lb. 9 oz.	2 oz.	.....	10	Occasionally first 5 days	4	
47	30	10	8	0.5	6	4	0.5	5	12	6 lb. 10 oz.	7 lb.	6 oz.	.....	10	Occasionally first 4 days	4	
48	21	10	?	....	1	11	....	7	13	5 lb. 15 oz.	6 lb. 4 oz.	5 oz.	.....	10	Occasionally 3-4-7-8 day	3	Complementary feedings
49	25	9	5	0.3	8	9	0.5	8	14	6 lb. 3 oz.	6 lb. 7½ oz.	7½ oz.	.....	10	Occasionally 2-9 day	3	
50	30	5	6	0.3	4	8	0.3	6	14	6 lb. 3 oz.	6 lb. 6 oz.	3 oz.	.....	10	Occasionally first 3 days and 8 day	4	
51	25	9	9	0.9	8	5	0.7	7	14	8 lb. 1 oz.	8 lb. 6 oz.	5 oz.	.....	10	Occasionally first 7 days	2	
52	26	7	10	0.4	..	4	0.4	..	14	6 lb. 6 oz.	6 lb. 12 oz.	6 oz.	.....	10	Occasionally first 5 days	2	
53	29	6	7	0.6	3	11	0.9	8	18	6 lb. 7 oz.	7 lb. 1 oz.	10 oz.	.....	10	Occasionally first 7 days	3	
54	27	9	10	0.8	..	8	0.7	..	18	7 lb. 4 oz.	7 lb. 13 oz.	9 oz.	.....	8	None	3	
55	26	10	9	0.2	8	12	0.5	..	21	6 lb. 14 oz.	7 lb.	2 oz.	.....	8	Occasionally first 3 days	4	

* Less than.

† Milk very toxic to Daphnia, accurate assay impossible.

In the group of heavy smokers (11 to 20 and more cigarets) the average concentration of nicotine in 11 specimens of milk obtained in the morning period was 0.445 mg. per liter and the average of 11 specimens obtained in the afternoon period was 0.5 mg. per liter. In this group the concentration of nicotine in 10 specimens of urine obtained in the morning period was 4.9 mg. per liter and the average in 8 specimens obtained in the afternoon period was 6.62 mg. per liter.

The constantly greater concentration of nicotine in the milk and urine obtained in the afternoon period was no doubt due to the continued excretion of some of the nicotine absorbed during the morning period in addition to that absorbed in the afternoon. This is in line with Emanuel's observation that the main excretion of nicotine appears in the milk and urine four to five hours after smoking. Approximately eleven to seventeen times as much nicotine was excreted in the urine as was excreted in the milk. The occasional lack of correlation between the number of cigarets smoked and the quantity of nicotine in the milk and urine noted in table 2 can be explained by the varied methods in which cigarets were smoked. In spite of the instructions to inhale or blow the smoke through the nostrils and to smoke each cigaret completely, it was difficult for the mothers to alter their smoking methods. Some would take but an occasional draw and permit the cigaret to be, for the most part, consumed between the fingers or on an ash tray. Others discarded the cigaret when but one half to three fourths used, while others would hold the cigaret constantly between the lips, thereby inhaling as much smoke as possible, down to the last half inch. It is interesting, therefore, that even with these varied smoking methods there was obtained so close a correlation between the number of cigarets smoked and the excretion of nicotine in the milk and urine.

EFFECT OF NICOTINE ON LACTATION

At the time of their discharge from the hospital, which occurred about the tenth day post partum, 11 of the 55 mothers who smoked failed to have enough breast milk for the needs of their babies (table 3). Of the 8 occasional smokers (1 to 4 cigarets), 2, or 25 per cent, failed. Of the 35 moderate smokers (6 to 10 cigarets), 8, or 22.8 per cent, failed, and of the 12 heavy smokers (11 to 20 or more cigarets) only 1, or 8.3 per cent, had insufficient milk. The other 44 mothers in this study had sufficient milk to nurse their infants successfully during their stay in the hospital, after which time they passed from our supervision.

Although the number of cases studied is relatively small, it is nevertheless interesting that the largest percentage of women who failed to nurse their infants successfully occurred in the group of occasional smokers, while a lesser percentage occurred in the group of moderate smokers and the least percentage in the group of heavy smokers. There was no significant difference, however, between the number of failures in the various groups on application of the chi square test. If, as shown by Hatcher and Crosby, nicotine suppresses lactation, the largest number of failures should have occurred in the group of heavy smokers. It is our impression, however, that the number of mothers who smoked cigarets and who failed to nurse their infants successfully was no greater than in the nonsmoking group at this hospital, although no comparative statistical study was made.

EFFECT OF NICOTINE ON THE NURSLING

In this study the keen interest and cooperation of the nursing personnel made it possible to obtain unusually careful and thorough records of the nurslings. Every untoward symptom was noted on the infants' charts, even though it was but an occasional regurgitation of a mouthful of milk. As a consequence, an analysis of the records determined that only 2 of the 55 infants failed to regurgitate or vomit some time during their hospital stay (table 2).

The regurgitation and vomiting occurred, for the most part, during the first four days of life, after which it gradually ceased. It was not severe, except in infant 1, in whom persistent vomiting occurred for the first three days and only occasional vomiting thereafter. This infant, who was entirely breast fed, was, nevertheless, 5 ounces (142 Gm.) over its birth weight at the end of nine days.

In contrast to the records of the 55 infants of mothers who smoked cigarets, the records, chosen at random of 55 infants of nonsmoking mothers failed to show any notation with regard to regurgitation and vomiting unless it was severe, because, as stated by the nurse in charge, occasional regurgitation and vomiting was of such common occurrence that it was considered almost normal.

Regurgitation and vomiting is indeed a common occurrence during the newborn period and is due to so many causes that it is quite difficult always to determine the specific cause. Whether the nicotine in the milk caused the occasional regurgitation and vomiting in the nurslings of smoking mothers is extremely doubtful, for in all the infants it had practically ceased while they still were ingesting milk containing nicotine. It is of particular interest that 1 of the 2 infants who did not regurgitate or vomit (case 54) was the offspring of a mother who smoked 18 cigarets over a twelve hour period and whose milk contained the high average nicotine concentration of 0.75 mg. per liter.

The bowel movements of all the nurslings of mothers who smoked cigarets were carefully examined for any abnormalities and a record was kept of the number of them. In no instance was either an abnormal or an excessive number of bowel movements observed. Toxic effects from nicotine such as irritability, exces-

TABLE 3.—*Effect of Cigaret Smoking on Lactation During Period of Study (Nine to Thirteen Days)*

	Number	Adequate Lactation	Inadequate Lactation	Failures, per Cent *
Occasional smokers (1-4 cigarets)	8	6	2	25.0
Moderate smokers (5-10 cigarets)	35	27	8	22.8
Heavy smokers (11-20+ cigarets)	12	11	1	8.3

* There was no significant statistical difference between the number of failures in the various groups on application of the chi square test.

TABLE 4.—*Average Gain and Loss of Nurslings at Time of Discharge (Ninth to Thirteenth Day)*

	Number	Gain	Number	Loss	Same as Birth Weight
Occasional smokers (1-4 cigarets)	4	5 oz.	1	2 oz.	1
Moderate smokers (5-10 cigarets)	21	5.8 oz.	5	3.6 oz.	
	1	Premature 31 oz.			
Heavy smokers (11-20+ cigarets)	11	6 oz.			

sive crying, lassitude and pallor were never noticed; in fact, it was the unanimous opinion of the nurses caring for these infants that they were as normal as the infants of nonsmoking mothers.

The gains and losses in weight of the nurslings of mothers who smoke cigarets are perhaps the most important criterion on which to base the effect of the nicotine in the milk (table 4). Of the 55 nurslings, 44 were solely breast fed and 11 received complementary feeding of cow's milk.

Of the 44 infants, 37 were above, 6 were below and 1 was at its birth weight at the time of discharge from the hospital, which occurred between nine and thirteen days after birth.

Of the 6 nurslings of mothers in the group of occasional smokers, 4 had gained an average of 5 ounces (142 Gm.), 1 had lost 2 ounces (57 Gm.) and 1 was at its birth weight at the time of discharge.

Of the 27 nurslings of mothers in the group of moderate smokers, 21 had gained an average of 5⅕ ounces (162 Gm.), 1 premature infant had gained the remarkable total of 1 pound and 15 ounces (879 Gm.) and 5 had lost an average of 3⅗ ounces (102 Gm.) at the time of discharge.

Of the 11 nurslings of mothers in the group of heavy smokers, all had gained an average of 6 ounces (170 Gm.).

TABLE 5.—*Average Gain and Loss of Nurslings on Complementary Feedings at Time of Discharge (Ninth to Thirteenth Day)*

Number	Gain	Number	Loss
9	4.7 oz.	2	2.2 oz.

Of the 11 infants who were on complementary feedings (table 5), 9 had gained an average of 4 7/10 ounces (133 Gm.) and 2 had lost an average of 2⅕ ounces (62 Gm.).

Without doubt this analysis indicates that nicotine has little, if any, effect on the ability of an infant to gain weight. It is interesting to note not only that all the nurslings of mothers in the group of heavy smokers gained but that their average gain was slightly more than the nurslings of mothers in the groups of occasional and moderate smokers.

COMMENT

The ease with which Daphnia could be observed in the milk and urine and compared with the control solutions of nicotine permitted accurate estimations.[15]

Our estimations, however, yielded much higher figures than those of Hatcher and Crosby and of Emanuel. The former, using the frog method, found less than 0.015 mg. of nicotine in the milk after smoking, and the latter, using leech segments, found a maximum of 0.03 mg. of nicotine per liter of milk after smoking 7 to 15 cigarets.

Whether our average figures, which ranged from 0.116 mg. to 0.5 mg. of nicotine per liter of milk, depending on the number of cigarets smoked, were due to the Daphnia method of bioassay is difficult to say, as comparative assays with other biologic methods were not made. Our figures certainly would have been lower had the night specimens, which contained very little nicotine, been pooled with those of the day specimens, when practically all of the smoking was done.

15. Vieburver, Arno: Daphnia the Biologic Reagent, J. Am. Pharm. A. 26:1112-1117 (Dec.) 1936.

The quantity of nicotine that would produce toxic effects in an infant is not known. Schroff, according to Emanuel, demonstrated on himself that the first toxic symptoms appear after the intake of 1 to 4 mg. of nicotine. A comparable intake for an infant of 6 to 7 pounds (2,722 to 3,175 Gm.) would therefore be in the neighborhood of 0.05 to 0.2 mg. If the infants in our study could, theoretically, have ingested at one time an entire liter of milk containing the concentration of nicotine found present in the specimens assayed, they would have obtained considerably more than the toxic dose of Schroff. They obtained, however, but 200 to 500 cc. of milk during a twenty-four hour period. Consequently, the actual amounts of nicotine ingested at a feeding were, in practically all, below the toxic threshold.

The absence of any demonstrable deleterious effect of nicotine on lactation and on the infants may be due also to the development of a tolerance to the drug. The development of tolerance to nicotine by smokers is well known. As all the mothers had smoked before, during and after their pregnancies, they unquestionably had a high tolerance to nicotine. The infants, exposed to the nicotine in their mother's blood while in utero, likewise had the opportunity to develop a tolerance to it—practically from the time that they were conceived. Behrend and Thienes[16] have shown experimentally that tolerance to nicotine can develop. They demonstrated that tolerance to the minimal effective dose and minimal convulsive dose can develop in young rats and that adult rats do not develop a tolerance to the fatal dose of nicotine.

The physiologic process involved in the development of nicotine tolerance was shown by Werle,[17] who found that the unexcreted portion of nicotine in the body is destroyed chiefly by the liver and that the kidneys and lungs as well as the liver of rabbits contain an enzymic system capable of detoxifying nicotine.

Dixon and Lee[18] also found that the livers of habituated animals destroyed nicotine somewhat more rapidly than those of the nonhabituated ones.

The factor of tolerance to nicotine must therefore be taken into consideration before the effect of this drug on man and animals can be evaluated properly.

CONCLUSIONS

1. Nicotine was excreted in the milk and urine of all the mothers who smoked cigarets.

2. Much larger quantities of nicotine were excreted in the urine than in the milk.

3. There was a definite correlation between the quantity of nicotine excreted in the milk and urine and the number of cigarets smoked.

4. Lactation was little, if at all, affected by the smoking of cigarets.

5. The nurslings were apparently unaffected by the quantity of nicotine that they ingested with the milk.

6. A tolerance to nicotine may be a factor which prevents this toxic drug from affecting the infants and the lactating ability of the mothers.

1904 Franklin Street—235 South Fifteenth Street.

16. Behrend, A., and Thienes, C. H.: Development of Tolerance to Nicotine by Rats, J. Pharmacol. & Exper. Therap. 48:317-325 (July) 1933.

17. Werle, E.: Ueber die Entgiftung von Nicotin durch tierisches Gewebe, Biochem. Ztschr. 288:268-272, 1936.

18. Dixon, W. E., and Lee, W. E.: Tolerance to Nicotine, Quart. J. Exper. Physiol. 5:373-383, 1912.

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ABSTRACT OF DISCUSSION

DR. WILLIAM BENROW THOMPSON, Los Angeles: Dr. Perlman and his co-workers have carefully assayed the nicotine content of the breast milk of 55 mothers who continued their smoking habits. It is highly significant that they detected nicotine in every instance in which the milk came from a woman who smoked, and that they failed to obtain a positive reaction when smoking had not been a factor. It is likewise significant that the values determined increased in direct proportion to the amount of smoking. It is evident that these values are small, and probably below the threshold of toxic effect on even immature infants. At least it is true that no toxic reactions were observed. Within the last few years there has been vast improvement in biologic assays. The detection of nicotine, in particular, is much more delicate with the use of Daphnia than with the use of frogs or leeches, and the estimation of amounts is less susceptible to experimental error. While one cannot assume that the skim milk would contain less nicotine than the cream, this probably is the case, since nicotine is more soluble in oil than in water. If that should be true, these reported amounts of nicotine would be increased somewhat. In this failure to utilize the entire milk output lies the only point wherein my own report may be deemed superior. The most startling feature of this study was that 44 of 55 mothers left the hospital with their babies entirely on breast feeding. I was so impressed that I went back over the records of 150 deliveries in which the mothers had been in for their six weeks check-ups, divided equally between primiparas and multiparas. On discharge from the hospital at twelve to fourteen days there were 16 primiparas and 6 multiparas feeding their babies, and 22 primiparas and 26 multiparas using complementary feedings. At six weeks even these figures had shrunk to 9 primiparas and 9 multiparas with an adequate supply, and 5 primiparas and 7 multiparas with partial feeding. At six weeks, then, only 30 to 20 per cent of these mothers were making any effort at lactation. Of this group, among the primiparas there were 33 who were nonsmokers at the time their histories were taken, although 7 had recently stopped because of nausea. Eight were light smokers, 7 were moderate and 27 were heavy smokers. The impressions of the earlier investigators, including myself, are confirmed by Perlman and his co-workers in that the amounts of nicotine thus excreted are so infinitesimal that they cannot logically be the basis for the usual and average disturbances of the infant digestive tract. While the minute quantities present in the milk of even a heavy smoker cannot be shown to have any deleterious effect, certainly it cannot be proved to be beneficial.

DR. A. M. DANNENBERG, Philadelphia: I am glad that Dr. Thompson brought up the question of the fat in the milk. In our study it was necessary for us to remove the fat in order that the daphnia would have a less dense medium in which to swim. We tried many ways to prepare the milk. It was filtered through felt, silica gel, glass wool and other filters but, unfortunately, these methods were not so satisfactory as the method adopted for our study. It was found through experiment that the nicotine concentration in breast milk was not altered by removing the cream. Lest some may think that we have an unusual group of lactating mothers in our hospital, I wish to state that this study was carried out over a period of three years, and it took all of that time to obtain 55 mothers with an apparent adequate supply of milk to cooperate in this study.

What Happens in Shock?—When a person passes into a condition of shock the sequence of events has been as follows: first, the trapping of a certain volume of blood in the capillary areas, nervous influence, cold, and toxemia from bruised and damaged muscle being the principal influences in producing the change; second, a fall in blood pressure as the result of the reduction in blood volume; third, deficient oxidation of tissue in the area where capillary stasis is occurring; and, fourth, a condition of acidosis resulting from a fall in the alkali reserve of the tissue and a corresponding rise in the carbon dioxide content of the blood plasma.—Fraser, Sir John, Shock and Hemorrhage, from War and the Doctor, edited by J. M. Mackintosh, M.D., Baltimore, William Wood & Co., 1942.

A PREPARATION FROM SPOILED SWEET CLOVER

[3,3'-METHYLENE-BIS-(4-HYDROXYCOUMARIN)] WHICH PROLONGS COAGULATION AND PROTHROMBIN TIME OF THE BLOOD: A CLINICAL STUDY

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It has been known for many years by veterinarians and cattle raisers that cattle fairly frequently and for no apparent reason bleed considerably and perhaps fatally. Studies of this condition were made originally and independently in 1921 by Schofield[1] in Canada and by Roderick[2] in this country. They determined that this hemorrhagic disease arises from eating improperly cured hay or silage made from the common sweet clovers. It was recognized early that if the hemorrhagic manifestations had not proceeded too far the hemorrhage could be controlled by withdrawal of the spoiled hay from the diet or by the injection of freshly drawn blood serum of healthy animals.[3] At first it was thought that the liver was damaged by the ingested spoiled hay, but this could not be confirmed by Roderick. However, he noted that the delayed coagulability of the blood involved a reduction in the prothrombin content of the blood and that this diminution paralleled the delay in the coagulation time.[4] This observation was confirmed later by Quick.[5] Roderick did not find any significant changes in the urine of the diseased cattle. The chemical constituents of the blood were found to be normal.[6]

Since 1934 Prof. Karl Paul Link and his associates of the Wisconsin Agricultural Experiment Station at the University of Wisconsin have been attempting to obtain the active hemorrhagic agent from spoiled clover. The story of this work has been unfolded in a series of brilliant reports,[7] finally crowned with the reports in

From the Division of Medicine (Drs. Allen and Barker) and the Division of Surgery (Dr. Waugh), the Mayo Clinic.

Because of lack of space, this article has been abbreviated for publication in THE JOURNAL. The complete article appears in the authors' reprints.

Drs. E. A. Hines Jr. and W. F. Kvale gave clinical help. Miss Margaret Hurn performed numerous prothrombin time tests and members of the surgical and medical staffs of the Mayo Clinic cooperated in this study.

Read before the joint meeting of the Section on Practice of Medicine and the Section on Experimental Medicine and Therapeutics at the Ninety-Third Annual Session of the American Medical Association, Atlantic City, N. J., June 12, 1942.

1. Schofield, F. W.: Canad. Vet. Rec. 2: 74, 1922; footnote 3.
2. Roderick, L. M.: The Pathology of Sweet Clover Disease in Cattle, J. Am. Vet. M. A. 74: 314-325 (Feb.) 1929.
3. Schofield, F. W.: Damaged Sweet Clover: The Cause of a New Disease in Cattle Simulating Hemorrhagic Septicemia and Blackleg, J. Am. Vet. M. A. 64: 553-572 (Feb.) 1924.
4. Roderick, L. M., and Schalk, A. L.: North Dakota Agric. Experiment Station Bull. 250, 1931. Roderick (footnotes 2 and 6).
5. Quick, A. J.: The Coagulation Defect in Sweet Clover Disease and in the Hemorrhagic Chick Disease of Dietary Origin, Am. J. Physiol. 118: 260-271 (Feb.) 1937.
6. Roderick, L. M.: A Problem in the Coagulation in the Blood; "Sweet Clover Disease of Cattle," Am. J. Physiol. 90: 413-425 (Feb.) 1931.
7. Campbell, H. A.; Roberts, W. L.; Smith, W. K., and Link, K. P.: Studies of the Hemorrhagic Sweet Clover Disease: I. The Preparation of Hemorrhagic Concentrates, J. Biol. Chem. 138: 47-55 (Oct.) 1940. Campbell, H. A.; Smith, W. K.; Roberts, W. L., and Link, K. P.: Studies on the Hemorrhagic Sweet Clover Disease: II. The Bioassay of Hemorrhagic Concentrates by Following the Prothrombin Level in the Plasma of Rabbit Blood, ibid. 138: 1-20 (March) 1941. Campbell, H. A.; Smith, W. K.; Overman, R. S., and Link, K. P.: Unpublished data.

March and April of 1941 of the isolation and synthesis of the hemorrhagic agent.[8] Additional studies were reported in 1942.[9]

Professor Link and his associates have been most generous in replying to our inquiries and in allowing us to study some of their work before publication. In April 1941 they sent us promptly some of the synthetic compound. We believed that the preparation might be used advantageously in place of heparin, which we and others have used clinically with benefit. The disadvantages of heparin are (1) the cost of its use (about $10 daily), (2) the need for continuous intravenous infusion or repeated intravenous injection and (3) the difficulty of maintaining a constant effect on coagulation time. A study of the effect of dicoumarin on dogs was begun about the middle of April 1941, and on May 9, 1941 we first administered the compound to a human being after it had been determined that the amounts administered in all probability would not cause any untoward effects. After some preliminary study an intensive program was begun to determine whether or not the preparation would prevent intravascular thrombosis in patients.

The hemorrhagic agent employed was dicoumarin [3,3'-methylene-bis-(4-hydroxycoumarin)] prepared by the method described by Campbell and Link. The compound is white, crystalline and only slightly soluble in water, but it is readily soluble in alkaline solutions. The drug was supplied to us by Abbott Laboratories and was administered by mouth in standard gelatin capsules, each of which contains 100 mg.

Two of our associates and one of us (Allen) first published the results of clinical studies on this preparation [10] in June 1941.[11] A report of further experiences by two of us (Barker and Allen), Butt and Bollman was given before the Central Society for Clinical Research in Chicago on Nov. 7, 1941. An abstract of this report was published in March.[12] The report of Bingham, Meyer and Pohle, published in October 1941, indicates that Link had given them dicoumarin for a study of its pharmacologic and clinical properties in September 1940.[13] An abstract of a second report by these authors [13a] was given before the Central Society for Clinical Research on November 7, and a subsequent report has been made by Meyer, Bingham and Axelrod.[14] Other reports on the effects of dicoumarin on human beings have been made by Townsend and Mills,[15] Stats and Bullowa [15a] and Prandoni and Wright.[15b]

In our study the prothrombin time for the blood of patients was determined by Magath's [16] modification of the method devised by Quick and his associates.[17] In some instances the coagulation time of human blood was measured by the method described by Murray and Janes,[18] and in others the method of Lee and White [19] was employed. Other tests were carried out in the usual manner.

EFFECTS OF DICOUMARIN

The effect of dicoumarin seems to be on prothrombin only. The prolongation of prothrombin time indicates the destruction of prothrombin or the suppression of its action or inhibition of the formation of prothrombin. Something in the body is necessary for the action of dicoumarin because if dicoumarin is added to drawn blood the prothrombin time is not influenced.[13] Coagulation time may be prolonged as a result of administration of dicoumarin, but determination of it is not a satisfactory method of measuring the activity of dicoumarin.

TABLE 1.—*Effect of Postoperative Administration of Dicoumarin on the Blood*

Cases	Prothrombin Time, Seconds	Bleeding Time, Minutes	Clot Retraction	Sedimentation Rate, Mm. in First Hour	Platelets per Cubic Millimeter of Blood
1	42	2½	None in 7 hours	...	282,000
2	58	2	Partial in 3 hours, complete in 7 hours	148	194,000
3	62	3½	6 hours	73	237,000
4	76	...	Partial in 4 hours, incomplete in 24 hours	90	
5	62	3	Complete in 2½ hours	60	120,000
6	51	3½	Complete in 6 hours	92	334,000
7	86	...	8 hours	145	
8	31	7	Complete in 1½ hours	100	176,000
9	65	2½	Complete in 1½ hours	100	223,000
10	33	5	Complete in 1½ hours	69	202,000

The studies of Bollman on animals, of Bingham, Meyer and Pohle on human beings and our own studies [20] indicate that hepatic function, the composition of urine, the value for blood sugar, the erythrocyte and leukocyte counts, the concentration of bilirubin and calcium in the serum, the value for the nonprotein nitrogen in the blood, the icteric index and the fragility of the erythrocytes and blood platelets are uninfluenced when dicoumarin is administered. As a part of our present

8. Campbell, H. A., and Link, K. P.: Studies on the Hemorrhagic Sweet Clover Disease: IV. The Isolation and Crystallization of the Hemorrhagic Agent, J. Biol. Chem. **138:** 21-33 (March) 1941. Stahmann, M. A.; Huebner, C. F., and Link, K. P.: Studies on the Hemorrhagic Sweet Clover Disease: V. Identification and Synthesis of the Hemorrhagic Agent, ibid. **138:** 513-527 (April) 1941. Huebner, C. F., and Link, K. P.: Studies on the Hemorrhagic Sweet Clover Disease: VI. The Synthesis of the Delta-Diketone Derived from the Hemorrhagic Agent Through Alkaline Degradation, ibid. **138:** 529-534 (April) 1941.

9. Overman, R. S.; Stahmann, M. A.; Sullivan, W. R.; Huebner, C. F.; Campbell, H. A., and Link, K. P.: Studies on Hemorrhagic Sweet Clover Disease: VII. The Effect of 3,3'-Methylene-Bis-(4-Hydroxycoumarin) on the Prothrombin Time of the Plasma of Various Animals, J. Biol. Chem. **142:** 941-955 (Feb.) 1942.

10. The name of this hemorrhagic agent as published in the title is too cumbersome for ordinary use. We do not like the term "hemorrhagic agent" for common usage because it may be used repeatedly without inducing hemorrhage. We use the name "dicoumarin," recognizing that the dicoumarin is a "family" name applying to related compounds and that the hemorrhagic agent is a dicoumarin. Hence in this paper the term dicoumarin applies to the hemorrhagic agent correctly described in the title of this presentation. More recently the term "dicumarol" has been advocated, and it is probable that this name will be adopted universally.

11. Butt, H. R.; Allen, E. V., and Bollman, J. L.: A Preparation from Spoiled Sweet Clover [3,3'-Methylene-Bis-(4-Hydroxycoumarin)] Which Prolongs Coagulation and Prothrombin Time of the Blood: Preliminary Reports of Experimental and Clinical Studies, Proc. Staff Meet., Mayo Clin. **16:** 388-393 (June 18) 1941.

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13. Bingham, J. B.; Meyer, O. O., and Pohle, F. J.: Studies on the Hemorrhagic Agent 3,3'-Methylene-Bis-(4-Hydroxycoumarin): I. Its Effect on the Prothrombin and Coagulation Time of the Blood of Dogs and Humans, Am. J. M. Sc. **202:** 563-578 (Oct.) 1941.

13a. Meyer, O. O.; Bingham, J. B., and Pohle, F. J.: The Effect of the Synthetic Dicoumarin, 3'3-Methylene-Bis-(4-Hydroxycoumarin) on the Prothrombin Time and Coagulation Time, J. A. M. A. **118:** 1063 (March 21) 1942.

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15a. Stats, Daniel, and Bullowa, J. G. M.: Effect of a Single Dose of 3,3'-Methylene-Bis-(4-Hydroxycoumarin) on Blood Coagulation in Humans, Proc. Soc. Exper. Biol. & Med. **50:** 66-70 (May) 1942.

15b. Prandoni, Andrew, and Wright, Irving: The Anticoagulants Heparin and the Dicoumarin-3,3'-Methylene-Bis-(4-Hydroxycoumarin), Bull. New York Acad. Med. **18:** 433-458 (July) 1942.

16. Magath, T. B.: Technic of the Prothrombin Time Determination, Am. J. Clin. Path. (Tech. Suppl.) **3:** 187-189 (Sept.) 1939.

17. Quick, A. J.; Stanley-Brown, Margaret, and Bancroft, F. W.: A Study of the Coagulation Defect in Hemophilia and in Jaundice, Am. J. M. Sc. **190:** 501-511 (Oct.) 1935.

18. Murray, Gordon, and Janes, J. M.: Prevention of Acute Failure of Circulation Following Injuries to Large Arteries: Experiments with Glass Cannulas Kept Patent by Administration of Heparin, Brit. M. J. **2:** 6-7 (July 6) 1940.

19. Todd, J. C., and Sanford, A. H.: Clinical Diagnosis by Laboratory Methods: A Working Manual of Clinical Pathology, ed. 9, Philadelphia, W. B. Saunders Company, 1939, p. 208.

20. Butt, Allen and Bollman.[11] Barker, Butt, Allen and Bollman.[12]

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study we have determined that the bleeding time is not influenced by dicoumarin as used clinically. The sedimentation rate of erythrocytes is almost routinely increased. There is definite retardation of clot retraction in many instances, but this is an inconstant finding (table 1). In the 10 cases in which the clot retraction and sedimentation rates were studied, dicoumarin was administered prophylactically after operation.

Bingham, Meyer and Pohle noted only moderate hydropic degeneration of the liver when dogs were given fatal doses of dicoumarin. Bollman has given dicoumarin repeatedly and for long periods to animals. According to him, hemorrhage occurs when large doses are given and when the prothrombin in the blood is greatly depleted, but the structures of the liver, kidneys and other vital structures are unchanged unless hemorrhage into them has occurred. Bingham and his associates reported that "Therapeutic and fatal doses of this material given to dogs did not produce significant pathologic changes in the liver or other parenchymatous organs but did, in many instances, produce capillary, arteriolar and venule dilatations." Rose, Harris and Chen [20a] observed that fatal doses of dicoumarin produced hemorrhage in various organs and tissues and also caused pulmonary edema. They found central necrosis of the liver in about half of the rats used in their study, but this was observed only occasionally among rabbits, mice and dogs that were used. In 4 cases we did not observe any significant alteration of hepatic function or in the concentration of serum bilirubin during or after administration of dicoumarin for short periods of time (one to two weeks).[11] Naturally one cannot conclude from short term studies such as this that dicoumarin is not harmful; similar results should be noted after administration for long periods of time before such conclusions can be drawn. In this connection, the studies of Link reported in conversation are interesting and valuable. Animals given dicoumarin or fed spoiled sweet clover hay repeatedly over a period of six or seven years so that the prothrombin time of their blood was increased (dicoumarin effect) about half of the time were well at the end of this time. They died of old age, as did those animals of similar age which had not received dicoumarin, and at necropsy there was no gross evidence of disease. The evidence from all these studies seems quite conclusive; dicoumarin inhibits the action of prothrombin by destroying it or by inhibiting its production. Secondary effects are interference with normal clot retraction and increased rate of sedimentation of erythrocytes. If enough dicoumarin is given, coagulation time is prolonged and bleeding may occur. In this connection, as we will emphasize later (except in cases of subacute bacterial endocarditis), the danger of bleeding is minimal unless the prothrombin time is greatly prolonged. Patients are ordinarily unaware of any effects of the drug. Urticaria and headache resulted in 1 case.

ROUTES OF ADMINISTRATION: THE LATENT PERIOD

We have given dicoumarin orally to all our patients. Under these circumstances there is a lag or latent period between the administration and the appearance of the effect. This lag is usually twenty-four to forty-eight hours. The disodium salt has been given intravenously by Bingham and his associates, who expressed the opinion that 4 to 5 mg. for each kilogram of body weight may be given intravenously to patients with safety.[12] Link has informed us in conversation that there is a latent period between the time of intravenous injection and the action on prothrombin time which is about the same as when dicoumarin is administered orally. The only advantages of intravenous administration, therefore, would seem to be (1) prevention of irregular effect owing to irregular absorption from the gastrointestinal tract and (2) use in instances in which the oral route cannot be used, as for example after operations on the gastrointestinal tract. At present a stable preparation for intravenous injection is not available. The effectiveness of the drug when given rectally and by inunction into the skin is being studied.

DICOUMARIN SHOULD BE ADMINISTERED ONLY IF THE PROTHROMBIN TIME CAN BE DETERMINED REPEATEDLY

It is well to emphasize here that dicoumarin is a hemorrhagic agent which may produce dangerous hemorrhage unless its administration is controlled rigidly. The amount of drug administered must depend on the prothrombin time. Hence, at present, dicoumarin should not be given unless the prothromin time can be determined. It is our opinion that the Quick method, as modified by Magath, is satisfactory. With this method the prothrombin time can be determined accurately by experienced technicians after a little practice.

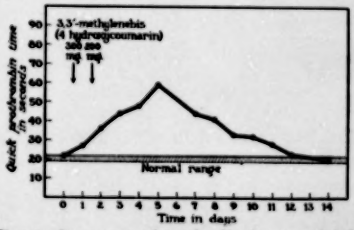

Chart 2.—Strong response by prothrombin time to a relatively small amount of dicoumarin administered orally.

At present, determinations of the prothrombin time are made on the blood of each patient each day, but, as experience is gained, we believe that administration may be successfully controlled in most cases if such studies are performed every two or three days. In the future a pattern of reaction to a specified amount of dicoumarin may be established, particularly if it is given intravenously. Under these circumstances determinations of the prothrombin time might be needed rarely. At present, however, we cannot recommend departure from the plan of determining the prothrombin time daily when dicoumarin is being administered.

METHOD OF ADMINISTRATION OF DICOUMARIN

We have given our patients single doses of 200 or 300 mg. of dicoumarin on the first day and 200 mg. on the second day. Subsequent to the first and second days decision relative to administration of dicoumarin is deferred until the prothrombin time of the blood drawn on that day is known. In our experience it is desirable to administer dicoumarin so as to keep the prothrombin time between thirty-five and sixty seconds. Because of apparent irregularities of absorption and differences in the sensitivity in different cases, no ratio has been established between the body weight

20a. Rose, C. L.; Harris, P. N., and Chen, K. K.: Toxicity of 3,3'-Methylene-Bis-(4-Hydroxycoumarin), Proc. Soc. Exper. Biol. & Med. **50**: 229-232 (June) 1942.

and the dosage.[21] If on the morning of the third day the prothrombin time exceeds 35 seconds, dicoumarin is not given on that day. If the prothrombin time is less than 35 seconds on the morning of the third day, 200 mg. is administered in a single dose. On each subsequent day, a similar plan is followed. Administration is continued as long as the effect of dicoumarin is desired. When administration of dicoumarin is discontinued, the prothrombin time remains elevated for a variable period and then gradually returns to normal. The time required for this return to normal varies from two to ten days but is usually three to seven days. It is apparent then that, unlike the situation when heparin is administered intravenously, the effect of dicoumarin continues for several days after its administration has been discontinued.

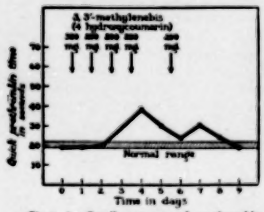

Chart 3.—Small response of prothrombin time to a relatively large amount of dicoumarin administered orally.

The response of the blood of different patients is variable. In some instances administration of 200 or 300 mg. on two successive days causes the prothrombin time to be elevated satisfactorily for several days (chart 2). In other instances the amount must be given daily for one, two or three additional days before there is a satisfactory effect on the prothrombin time (chart 3).

Our patients who have had operations and received dicoumarin as prophylaxis against thrombosis received dicoumarin beginning on the day following operation and over a sufficient period to assure elevation of the prothrombin time until they become active. Usually, dicoumarin is not given on or after the day on which the patient first sits on the edge of the bed. A satisfactory effect on prothrombin time is desired for about ten days after pulmonary embolism and for about ten days after the onset of acute thrombophlebitis. In other cases, administration of dicoumarin is arranged to meet the assumed needs of the particular situation.

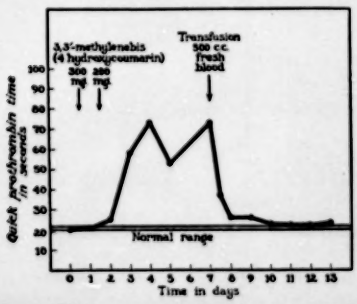

Chart 5.—Effect on prothrombin time of transfusion of fresh blood.

21. This phase of the problem, particularly when the disodium salt is given intravenously, needs more consideration than it has been given heretofore.

CONTROL OF THE EFFECT OF DICOUMARIN ON PROTHROMBIN TIME

Since the effect of dicoumarin on prothrombin time endures for some days after cessation of administration of dicoumarin, it is advisable to have some way to control the effect of the drug in case bleeding occurs. Clinical and experimental studies indicate that synthetic vitamin K is entirely or largely ineffective. Overman, Field, Baumann and Link [21a] have shown that the administration of tremendous doses of synthetic vitamin K to small animals reduces the prothrombin time elevated by administration of dicoumarin. However, in clinical practice no reliance can be placed on synthetic vitamin K. Transfusions of fresh whole blood or plasma reduce prothrombin time transiently or permanently (chart 6). We have not made any qualitative studies of the degree and persistence of this effect but sometimes it does not last more than a few hours. In clinical practice, we give a transfusion whenever alarming hemorrhage occurs. This has happened infrequently. If bleeding is not controlled, another transfusion is given and this is repeated until bleeding stops. When bleeding stops as a result of transfusion, it usually does not recur, although the prothrombin time may again be greatly increased after a temporary decrease. This is probably due to adequate coagulation during the period of decreased prothrombin time.

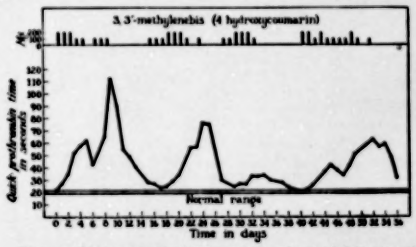

Chart 6.—Effect on prothrombin time of intermittent administration of dicoumarin.

THE COMBINED ADMINISTRATION OF HEPARIN AND DICOUMARIN

Since there is a latent period after administration of dicoumarin and before impairment of prothrombin time, this drug cannot be used when a quick anticoagulant effect on the blood is desired. Under these circumstances we give heparin intravenously and dicoumarin orally at the same time. Since heparin does not influence the prothrombin time, the effect of dicoumarin can be determined by determining the prothrombin time even when heparin is given at the same time. When the effect of dicoumarin is adequate, as determined by calculation of prothrombin time, administration of heparin is discontinued. It is not our purpose to consider the administration of heparin here. It is best given by continuous intravenous administration, but occasionally we give it by the method of Crafoord and Jorpes,[22] who inject 50 to 100 mg. directly into a vein

21a. Overman, R. S.; Field, J. B.; Baumann, C. A., and Link, K. P.: Studies on the Hemorrhagic Sweet Clover Disease: IX. The Effect of Diet and Vitamin K on the Hypoprothrombinemia Induced by 3,3'-Methylene-Bis-(4-Hydroxycoumarin) in the Rat, J. Nutrition **23**: 589-602 (June) 1942.

22. Crafoord, Clarence, and Jorpes, Erik: Heparin as a Prophylactic Against Thrombosis, J. A. M. A. **116**: 2931-2935 (June 28) 1941.

every six hours. Usually, such injections need to be continued for thirty-six to forty-eight hours, at which time dicoumarin has become effective.

THE EVIDENCE THAT DICOUMARIN LESSENS THE TENDENCY TO INTRAVASCULAR COAGULATION OF BLOOD

Clinical studies which will be reported later in this paper indicate that when the prothrombin time is increased by means of administration of dicoumarin, intravascular thrombosis does not ordinarily occur. Studies by Bollman and Preston [23] on animals indicate that this is true. Their studies indicate that glass cannulas interposed between two ends of an artery seldom are occluded by thrombi when animals have received dicoumarin. Venous thrombi which occurred regularly under a set of "normal" circumstances seldom occurred in animals that had received dicoumarin. In their experience, dicoumarin could be used in the laboratory to replace heparin in experiments in which intravascular coagulation of blood was to be avoided. By means of experiments on dogs, Dale and Jaques [23a] showed that the administration of dicoumarin decreases considerably the tendency to thrombosis in veins which have been crushed on a linen thread and also in glass cells inserted between the carotid artery and the jugular vein. Richards and Cortell [23b] have shown that after administration of dicoumarin there is pronounced inhibition of the formation of thrombi in veins into which a sclerosing solution, ethanolamine oleate, has been injected.

CONTRAINDICATIONS TO THE USE OF DICOUMARIN

Dicoumarin should not be used for patients who are bleeding. Our experience indicates that its use is particularly dangerous in subacute bacterial endocarditis. This probably results from the increased tendency of patients with subacute bacterial endocarditis to bleed from kidneys or into the brain even when dicoumarin is not used. The reported experiences with heparin indicates that there is also danger from using it in subacute bacterial endocarditis. The effect of dicoumarin on prothrombin time is excessive in cases of renal insufficiency or in those in which adequate amounts of urine are not excreted. It should be used very cautiously or not at all under these circumstances. Bollman and Preston's experiments indicate that renal failure enhances the effect of heparin tremendously. Naturally it should not be used in cases in which the prothrombin time is already prolonged (vitamin K deficiency).

TABLE 2.—*Effect of Dicoumarin: Occurrence of Venous and Arterial Thrombosis, Pulmonary Embolism and Bleeding*

Reason for Anticoagulant Therapy	Cases	Successful Elevation of Prothrombin Time (27+ Seconds)	Pulmonary Embolism or Infarction While Prothrombin Time Was Elevated	Arterial or Venous Thrombosis While Prothrombin Time Was Elevated	Bleeding		Deaths
					Major, Blood Transfusion Required	Minor	
Postoperative pulmonary embolism and infarction	70	67	1	1	2	2	2*
Postoperative thrombophlebitis	50	45	0	1	0	2	2†
Occurrence of thrombophlebitis or pulmonary embolism after previous operation	15	13	0	0	0	0	0
Abdominal hysterectomy‡	129	124	0	0	4	10	0
Other operations‡	78	74	0	0	5	1	1
Peripheral vascular disease	18	18	0	0	1	1	0
Acute coronary thrombosis	3	3	0	0	0	0	0
Subacute bacterial endocarditis	5	5	0	0	2	1	2
Total	368	349	1	2	14	17	7

* One death from uremia; one death from effects of large embolism which occurred before prothrombin time was elevated.
† One death from pneumonia; one death from peritonitis.
‡ No thrombosis or embolism; administration of dicoumarin started on second day after operation.

TABLE 3.—*Effect of Dicoumarin on Incidence of Venous Thrombosis and Pulmonary Embolism*

Reason for Anticoagulant Therapy	Adequate Elevation of Prothrombin Time	Subsequent Thrombosis or Embolism		Subsequent Embolism		Subsequent Fatal Embolism	
		Expected Number If Untreated	Actual Number	Expected Number If Untreated	Actual Number	Expected Number If Untreated	Actual Number
Postoperative pulmonary embolism or infarction	67	39	2*	20	1*	13	0
Postoperative thrombophlebitis	45	15	1	9	0	3	0
Thrombophlebitis or embolism complicating previous operations	13	5	0	3	0	1	0
Abdominal hysterectomy	124	6	0	3	0	0.9	0

* In 1 case thrombophlebitis developed when prothrombin time was 26 seconds. In 1 case embolism developed when prothrombin time was 25 seconds. Treatment with dicoumarin was considered inadequate in these cases.

RESULTS OF CLINICAL STUDIES

We have administered dicoumarin in 374 cases. Six of these cases were reported previously.[11] The indications for the use of the drug in the remaining 368 cases are shown in table 2. In these cases, dicoumarin was given in an effort to prevent arterial or venous thrombosis and pulmonary embolism or to prevent extension of intravascular thrombosis. Since we feel that an embolus is always a very recent thrombus or a portion of a very recent thrombus, prevention of extension of thrombosis is important. In the cases of postoperative pulmonary embolism, infarction and postoperative thrombophlebitis, the administration of the dicoumarin was begun as soon as the clinical diagnosis was made. In a few cases heparin was used until dicoumarin became effective. In cases in which thrombophlebitis or pulmonary embolism had complicated a previous operation and in cases in which abdominal hysterectomy or other operations were performed on patients who had not had thrombophlebitis or embolism, administration of dicoumarin was begun approximately twenty-four hours after the operation was performed. Slight elevation of the prothrombin time may be sufficient to

23. Bollman, J. L., and Preston, F. W.: Unpublished data.
23a. Dale, D. U., and Jaques, L. B.: The Prevention of Experimental Thrombosis by Dicoumarin, Canad. M. A. J. **46**: 546-548 (June) 1942.
23b. Richards, R. K., and Cortell, Ruth: Studies on the Anticoagulant 3,3'-Methylene-Bis-(4-Hydroxycoumarin), Proc. Soc. Exper. Biol. & Med. **50**: 237-242 (June) 1942.

prevent thrombosis, but it is probable that a definite elevation of the prothrombin time is necessary in many cases. Hence we desire to keep the prothrombin time between 35 and 60 seconds during the "danger period" in preventing intravascular thrombosis. Pulmonary infarction developed in 1 case in which the prothrombin time was 26 seconds (normal is 19 to 22 seconds) and thrombophlebitis developed in 1 case in which the prothrombin time was 35 seconds and in another case in which it was 45 seconds. However, these are the only 3 instances of clinical thrombosis which developed in the entire 374 cases during the time the prothrombin times were elevated. In our experience, bleeding of moderate or severe degree occurred only when the prothrombin time was above 60 seconds except in 2 cases.

The reasons for feeling that elevation of the prothrombin time as a result of administration of dicoumarin prevents thrombosis are summarized in table 3. In a statistical study of postoperative venous thrombosis and pulmonary embolism, Barker, Nygaard, Walters and Priestley[24] found that in cases of pulmonary embolism in which patients survived the chance of subsequent development of thrombophlebitis or pulmonary embolism during the next few weeks was 44 per cent, that the chance of subsequent development of embolism was 30 per cent and that the chance of the subsequent development of fatal embolism was 18.5 per cent. Although our series of 69 cases of postoperative pulmonary embolism in which dicoumarin produced adequate elevation of the prothrombin time is small, it is probably statistically significant that subsequent thrombosis developed in only 1 of these cases when the prothrombin time was elevated only to 26 seconds and that embolism did not develop in this group except in 1 case in which the prothrombin time was elevated only to 25 seconds. As stated previously, we feel that this effect of the dicoumarin is inadequate. The 45 cases of postoperative thrombophlebitis, 13 cases in which thrombophlebitis or embolism complicated previous operations and the 124 cases in which abdominal hysterectomy was performed are too small a series to warrant conclusions as to whether elevation of the prothrombin time by administration of dicoumarin really prevents thrombosis or not, although, as noted in the table, some instances of thrombophlebitis or pulmonary embolism could have been expected in these groups from a statistical standpoint.[23] In cases in which the drug was administered after operation, both those in which either venous thrombosis or embolism occurred and those in which neither thrombosis nor embolism occurred, the prothrombin time was kept elevated until the patient was ambulatory, that is, for seven to twenty-one days. In several of the cases of peripheral vascular disease, dicoumarin was given for a considerably longer period (table 4 and chart 6).

Because of the fact that bleeding occurs in animals poisoned with spoiled sweet clover and occasionally in laboratory animals that have received large doses of dicoumarin over long periods of time, and because of the known tendency of patients who have elevation of prothrombin time as a result of hepatic disease to bleed, our patients who received dicoumarin as anticoagulant therapy have been observed carefully for any evidence of hemorrhage even of minimal degree. Slight bleeding from the wound may occur occasionally after any operation, particularly if it involves the vagina. Hence, some of the bleeding that we have noted might have occurred anyway and may not have had anything to do with the administration of dicoumarin. We encountered bleeding in 31 cases, which are included in table 5. The bleeding was of a slight degree in 17 cases, of a moderate degree in 9 cases and of a severe degree in 5 cases. The bleeding was from the operative site in 24 cases, ecchymosis of the skin of the thigh developed in 2 cases, hematuria developed in 4 cases and nasal bleeding developed in 2 cases. A nasal tube had been used in 1 of these cases. Cerebral bleeding occurred in 3 cases; in 1 of these cases extensive hemorrhage occurred in many organs. In 3 cases the bleeding from the site of operation was severe and in 1 case it was

TABLE 4.—*Effect of Dicoumarin in Cases of Peripheral Vascular Disease*

Case	Disease	Total Dose of Dicoumarin, Mg.	Duration of Treatment with Dicoumarin, Days	Results
11	Diabetes mellitus; sudden arterial thrombosis of foot; cellulitis	700	11	Effect stopped by blood transfusion because of emergency amputation; prolonged bleeding from stump
12	Arteriosclerosis obliterans; sudden arterial thrombosis	2,800	30	Patient rather resistant to dicoumarin; no further thrombosis
13	Polycythemia; simple arterial thrombosis	2,600	24	Patient rather resistant to dicoumarin; no further thrombosis
14	Arteriosclerosis obliterans	2,400	30	Patient rather resistant to dicoumarin; no further thrombosis
15	Arteriosclerosis obliterans	800	9	No further thrombosis
16	Embolism of left femoral artery; hyperfunctioning adenomatous goiter; auricular fibrillation (posthyroidectomy)	1,200	19	Heparin also administered for first two days; excellent clinical result; no extension of thrombosis; no symptoms at time of dismissal; involved artery still pulseless
17	Embolism of right popliteal artery	800	14	Heparin administered first two days; no secondary thrombosis
18	Simple arterial thrombosis in right leg	1,000	11	No further thrombosis
19	Thromboangiitis obliterans	4,400	32	Patient very resistant to dicoumarin; progressive gangrene
20	Thromboangiitis obliterans	900	10	Patient sensitive to dicoumarin; prothrombin time increased to 240 seconds; slight amount of bleeding from stump on seventh day; effect stopped by blood transfusion
21	Thrombosis of cavernous sinus	500	5	Patient aged 9 years; no progression of thrombosis; effect stopped by blood transfusion because of anemia
22	Idiopathic thrombophlebitis; pulmonary embolism	500	9	Effect stopped because of hematuria and ecchymosis of thigh
23	Idiopathic thrombophlebitis	500	16	No further thrombosis
24	Idiopathic thrombophlebitis	1,400	12	No further thrombosis
25	Pylephlebitis	1,400	30	No further thrombosis
26	Thrombosis of cavernous sinus	900	5	No further thrombosis
27	Thrombophlebitis of superior vena cava	1,200	11	No further thrombosis
28	Arteriovenous fistula after excision	700	10	No thrombosis

24. Barker, N. W.; Nygaard, K. K.; Walters, Waltman, and Priestley, J. T.: A Statistical Study of Postoperative Venous Thrombosis and Pulmonary Embolism: III. Time of Occurrence During Postoperative Period, Proc. Staff Meet., Mayo Clin. **16**: 17-21 (Jan. 8) 1941.

fatal. As previously stated, it is doubtful whether dicoumarin was an etiologic factor in this case. Two other patients died, apparently as a result of hemorrhage. Both of these had subacute bacterial endocarditis. In 1 of these cases the clinical picture of cerebral hemorrhage developed. Necropsy was not done. A cerebral hemorrhage may occur spontaneously in cases of subacute bacterial endocarditis, but we must assume that elevation of the prothrombin time could have favored such a lesion. In another case of subacute bacterial endocarditis, in which sulfadiazine also was administered, anuria developed suddenly, and forty-eight hours later numerous ecchymoses developed in the skin and oral mucosa. Coma and death ensued. Necropsy revealed extensive hemorrhages in many organs and tissues. We feel that patients with subacute bacterial endocarditis have an increased tendency to bleed as a result of the disease and hence have a great deal more tendency to bleed when the prothrombin time is elevated than do patients in the other clinical groups that we have observed. There had not been any evidence of thrombosis or embolism in any of the 3 cases in which death was due to hemorrhage.

We have not found a correlation between the tendency to bleed and the exact levels of the prothrombin time, as we have seen prothrombin times of two or three minutes without any evidence of hemorrhage.

CONCLUSIONS

1. Dicoumarin when administered orally prolongs the prothrombin time, impairs clot retraction and increases the sedimentation rate of erythrocytes. Large amounts prolong the coagulation time. Hemorrhage may occur when dicoumarin has greatly prolonged the prothrombin time. The drug seems essentially harmless otherwise.

2. Dicoumarin should be administered only when its effect can be determined by repeated calculations of the prothrombin time.

3. The response of the prothrombin time of different patients is variable. In general, larger doses produce greater prolongation of prothrombin time than do smaller ones, and the effect endures longer.

4. A plan of administering 300 mg. on the first day, 200 mg. on the second day and 200 mg. on each day after the second on which the prothrombin time is less than 35 seconds has been used by us.

5. After administration of the first dose from twenty-four to forty-eight hours elapse before an effect on prothrombin time is noted. After discontinuation of administration, prothrombin time may be prolonged from two days to two or three weeks, depending on the amount given.

6. Heparin and dicoumarin may be administered together when both quick and prolonged action are desired. The use of heparin is discontinued when the prothrombin time has been satisfactorily prolonged by dicoumarin.

7. Synthetic vitamin K has little or no effect on prolongation of prothrombin time resulting from dicoumarin. Transfusion of fresh blood will reduce for variable periods the prothrombin time which has been increased by dicoumarin.

8. Clinical and experimental studies strongly suggest the value of administration of dicoumarin in preventing intravascular thrombosis.

9. The danger of hemorrhage from administration of dicoumarin serves as a constant emphasis for care in its use.

THE DICOUMARIN 3,3'-METHYLENE-BIS-(4-HYDROXYCOUMARIN)

ITS PHARMACOLOGIC AND THERAPEUTIC ACTION IN MAN

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AND
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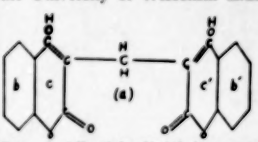
One of the most interesting and challenging developments in the field of the biologic sciences in recent years has been the recognition, isolation and, finally, synthesis of the substance causing hemorrhagic sweet clover disease in cattle, the dicoumarin 3,3'-methylene-bis-(4-hydroxycoumarin). We must give full credit for this contribution to two keen students of veterinary medicine, Schofield [1] and Roderick,[2] and to an outstanding agricultural chemist, Karl Paul Link. Schofield in Canada and Roderick at the North Dakota Agricultural Experimental Station studied and quite accurately analyzed the factors responsible for this phenomenon in cattle and rabbits. They pointed out that, whereas normal sweet clover silage produced no damage, spoiled sweet clover resulted in hemorrhagic tendencies and often in death. In 1934 Prof. Karl Paul Link and his associates at the Wisconsin Agricultural Experimental station of the University of Wisconsin undertook the



The dicoumarin 3,3'-methylene-bis-(4-hydroxycoumarin).

task of identifying the hemorrhagic factor in spoiled sweet clover.

This marked the beginning of a series of careful investigations, brought to fruition seven years later with the discovery that coumarin, the aromatic bitter tasting substance in sweet clover, is the compound that undergoes change when the hemorrhagic agent is formed in sweet clover spoilage.

In a series of brilliant reports [6] published, beginning in 1940, Link and his co-workers established that the hemorrhagic agent was a dicoumarin and succeeded in isolating, crystallizing and synthesizing the biologically active substance. More than one hundred and fifty compounds, either analogues or related in structure, have been prepared, of which forty have been shown to have prothrombin reducing properties. This discussion was conclusively demonstrated by Stahmann, Hueb-

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Owing to lack of space, this article has been abbreviated for publication in THE JOURNAL. The complete article appears in the authors' reprints.

Read before the joint meeting of the Section on Practice of Medicine and the Section on Experimental Medicine and Therapeutics at the Ninety-Third Annual Session of the American Medical Association, Atlantic City, N. J., June 12, 1942.

1. Schofield, F. W.: Canad. Vet. Rec. **2**: 74, 1922.

2. Roderick, L. M., and Schalk, A. L.: North Dakota Agricul. Experimental Station, Bull., 250, 1931. Roderick.[3]

6. Campbell, H. A.; Roberts, W. L.; Smith, W. K., and Link, K. P.: Studies on the Hemorrhagic Sweet Clover Disease: I. The Preparation of Hemorrhagic Concentrates, J. Biol. Chem. **136**: 47, (Oct.) 1940. Campbell, H. A.; Smith, W. K.; Roberts, W. L., and Link, K. P.: Studies on the Hemorrhagic Sweet Clover Disease: II. The Bioassay of Hemorrhagic Concentrates by Following the Prothrombin Level in the Plasma of Rabbit Bleed, ibid. **138**: 1-20 (March) 1941. Campbell, H. A., and Link, K. P.: Studies on the Hemorrhagic Sweet Clover Disease: IV. The Isolation and Crystallization of the Hemorrhagic Agent, ibid. **138**: 21, (March) 1941.

ner and Link [7] to be the dicoumarin 3,3'-methylene-bis-(4-hydroxycoumarin).

It was obvious that the isolation and synthesis of this dicoumarin, which could be prepared in quantity, would prove of interest to workers in the field of either vascular or blood diseases, and through the courtesy of Dr. Link several clinical groups have been studying its action in man during the past two years. Meyer, Bingham and Pohle [10] presented the first report on the action of this dicoumarin in man on Feb. 27, 1941. In June, Butt, Allen and Bollman [11] published a preliminary study of its use in dogs and a series of 6 in human beings. In October 1941 we presented our preliminary observations on the use of this substance [12] in a series of 20 human subjects.[13] Since that time further progress reports have been presented by each of these groups. Each group presented a report before the American Society for Clinical Investigation on May 4, 1942. In general, the observations of these three groups have been similar. All have found that in man, as in

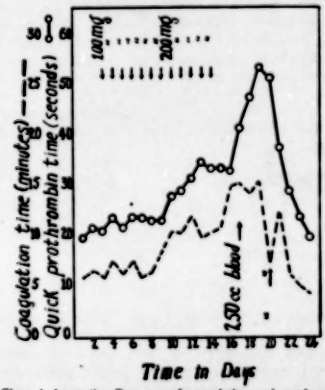

Chart 1 (case 4).—Response of coagulation and prothrombin times to administration of dicoumarin. The patient, aged 37, weighing 135 pounds, had a diagnosis of thromboangiitis obliterans.

lower animals, the administration of dicoumarin results in a prolongation in the prothrombin time and a delay in the coagulation of the blood. It was determined that there is a lag of from twenty-four to seventy-two hours before the action of the drug is measurable. Bingham, Meyer and Pohle [14] showed that this was true whether the substance was given orally or intravenously. All reported that fresh transfusions of serum or whole blood will cause prompt lowering of the prothrombin and coagulation times but that in some instances this effect is not sustained, thus necessitating several transfusions. We found that bank blood older than 96 hours had no effect, probably owing to loss in prothrombin activity. Each group of investigators was disappointed in the effect of vitamin K. In the dosage usually effectively employed in cases presenting prothrombin deficiency vitamin K consistently failed to produce any response toward normal in prothrombin deficiency due to dicoumarin.

In October 1941 we reported for the first time in man a hemorrhagic syndrome following the administration of the dicoumarin 3,3'-methylene-bis-(4-hydroxycoumarin).[12] This was essentially the same in its manifestations as the syndrome of hemorrhagic sweet clover disease. In 8 of our first 20 patients hemorrhagic manifestations were noted. A summary of these case histories will be found in table 1. There was a wide unexplained variation in the hemorrhagic response in different individuals. As noted in table 2, the dosage was comparable in the hemorrhagic and the nonhemorrhagic group in regard to both magnitude and duration of therapy. For example, patient 34 [15] in our series received a total of 8.1 Gm. of the drug, or 98.7 mg. per kilogram of body weight—the largest dose given without any toxic manifestations. Other patients received 3.6 Gm., 3.4 Gm., 3 Gm. and similar doses without ill effects. The following case reports are typical of the phenomenon as it occurs in man:

Case 4.—A man aged 37 weighing 135 pounds (61.2 Kg.), with a diagnosis of thromboangiitis obliterans and osteomyelitis of the left second toe, after a control period of seventy-two hours had a normal prothrombin time of 20 to 27 seconds and a coagulation time of 6 to 8 minutes. He received 100 mg. of dicoumarin every twenty-four hours. The first significant elevation in prothrombin time occurred seven days after inception of therapy, at which time the prothrombin time rose to 28 seconds. The coagulation time rose to 10 to 5 minutes on the same day. The total dose until then was 700 mg. The dose was then doubled (200 mg. every twenty-four hours). Prothrombin and coagulation times continued to increase during the subsequent period, the prothrombin time attaining 34 seconds and the coagulation time 10 minutes on the thirteenth day.

Dicoumarin was discontinued at this time because the patient's temperature had risen to 101 F. The pulse rate was 110 and the respiratory rate 24. The total dose of dicoumarin was 1,700 mg. Purpura appeared in the skin of the left leg and foot. The gums bled profusely. The patient complained of lumbar pain. A capillary fragility test (15 minutes midway between systolic and diastolic pressure) revealed ten petechiae (normal). The following day frank hematuria was associated with severe lumbar and testicular pain and dysuria. The urine appeared grossly to be practically pure blood. Brisk bleeding occurred from the osteomyelitis fistula at the tip of the second left toe. A transfusion of 4 day old citrated blood was secured from the blood bank. No donors of the patient's type were immediately available. After the transfusion his hemoglobin was 76 per cent, red blood cells 4,000,000, white blood cells 8,200, polymorphonuclear leukocytes 76 per cent, lymphocytes 32 per cent, monocytes 2 per cent. On the fourteenth day the coagulation time rose to 15 minutes and the prothrombin time to 32 seconds, subsequently rising to 15.5 minutes and 54 seconds respectively in the ensuing ninety-six hours. On one occasion the patient vomited coffee ground vomitus. The temperature remained elevated. Despite the transfusion, vitamin K and vitamin C therapy and adequate sedation, hemorrhagic manifestations persisted. In addition to these manifestations the patient had a large sublingual ecchymosis and bladder retention.

A second transfusion, this time of freshly obtained blood, was given on the seventeenth day, after which the hemorrhagic manifestations began to subside, and the prothrombin and coagulation times dropped to normal over a seventy-two hour

7. Stahmann, M. A.; Huebner, C. F., and Link, K. P.: Studies on the Hemorrhagic Sweet Clover Disease: V. Identification and Synthesis of the Hemorrhagic Agent, J. Biol. Chem. **138**: 513 (April) 1941.

10. Meyer, O.; Bingham, J. B., and Pohle, F. J.: Read before the University of Wisconsin Medical Society, Feb. 27, 1941.

11. Butt, H. R.; Allen, E. V., and Bollman, J. L.: A Preparation from Spoiled Sweet Clover [3,3'-Methylene-Bis-(4-Hydroxycumarin)] Which Prolongs Coagulation and Prothrombin Time of the Blood: Preliminary Report of Experimental and Clinical Studies, Proc. Staff Meet., Mayo Clin. **16**: 338 (June 18) 1941.

12. The dicoumarin used in our studies was supplied by Dr. K. P. Link of the University of Wisconsin and the Lederle Laboratories, Inc.

13. Prandoni, Andrew, and Wright, Irving: The Anti-Coagulants Heparin and the Dicoumarin 3,3'-Methylene-Bis-(4-Hydroxycoumarin) read before the Graduate Fortnight of the New York Academy of Medicine in October 1941, Bull. New York Acad. Med., July 1942.

14. Bingham, J. B.; Meyer, O. O., and Pohle, F. J.: Studies on the Hemorrhagic Agent 3,3'-Methylene-Bis-(4-Hydroxycoumarin): I. Its Effect on the Prothrombin and Coagulation Time of the Blood of Dogs and Humans, Am. J. M. Sc. **202**: 363 (Oct.) 1941.

15. Treated after table 2 was prepared.

period. On the nineteenth day a subconjunctival hemorrhage appeared and the hematuria had abated. The sublingual ecchymoses were resorbing. Microscopic hematuria persisted until the twentieth day, at which time the coagulation and prothrombin times attained normalcy. The total duration of the toxic manifestations was nine days.

In this case 1,700 mg. of dicoumarin, administered orally in twelve divided doses, resulted in prolongation of coagulation and prothrombin times. The first effect of the drugs was noted after seven days. Toxic hemorrhagic manifestations of nine days' duration included lumbar and testicular pain, hematuria, purpura, hematemesis, spontaneous bleeding from the wound site, sublingual ecchymoses, subconjunctival hemorrhages, dysuria, bladder retention and temperature elevation. Transfusion of 4 day old citrated blood did not influence the course of these manifestations, while a transfusion of freshly secured blood resulted in subsidence within seventy-two hours. Massive doses of vitamins C and K had no effect.

CASE 6.—A patient aged 60 weighing 127 pounds (57.6 Kg.), with a diagnosis of diabetes mellitus, arteriosclerotic endarteritis obliterans and osteomyelitis of the right hallux, after a control period of seven days had a prothrombin time of 20 seconds, a coagulation time of 7 to 9 minutes and a sedimentation rate of 72 mm. an hour.

Dicoumarin was administered in 200 mg. doses at twenty-four hour intervals over a period of twelve days. Three days after onset of therapy the prothrombin time rose to 27 seconds. The coagulation time showed no significant variation, however, until the seventh day after 1,400 mg. of the drug had been administered, at which time a definite upswing was noted reaching 9 minutes 25 seconds. Administration of the drug was discontinued on the twelfth day (2,200 mg. total). At this time the coagulation time was 13.5 minutes and the prothrombin time 28 seconds. Twenty-four hours later prolonged bleeding from minor lacerations sustained while shaving was noted. A capillary fragility test revealed 8 petechiae after fifteen minutes (normal). On the sixteenth day large ecchymoses involving both lumbar and inguinal regions were discovered on the right side. There was no associated lumbar costovertebral tenderness. The sedimentation rate rose from a previous reading of 75 to 132 mm. an hour. A recheck of the capillary fragility revealed no significant deviation from normal. Venipuncture, despite great care, produced extensive ecchymoses at the needle site. Prothrombin and coagulation times had by this time attained 40 seconds and 16 minutes respectively. Forty-eight hours later, on the eighteenth day, ecchymoses similar in character and distribution occurred on the contralateral left side. On the twenty-second day, ten days after the withdrawal of dicoumarin, both the coagulation and prothrombin curves began to descend, reaching normalcy on the twenty-ninth day. Ecchymoses showed progressive resorption, disappearing completely by the thirty-fourth day.

Administration of dicoumarin in doses of 200 mg. every twenty-four hours produced an elevation of the prothrombin time after 600 mg. had been administered and elevation of coagulation time after the administration of 1,400 mg. The capillary fragility revealed no significant deviation from normal. Venipuncture, despite great care, produced extensive ecchymoses at the needle site. Prothrombin or coagulation times attained 40 seconds and 16 minutes respectively. A total of 2,200 mg. of the drug was given over a 12 day period. Twenty-four hours after the withdrawal of medication hemorrhagic manifestations appeared in the form of spontaneous bleeding from the wound in the right hallux. Other manifestations were huge ecchymoses in both lumbar and inguinal regions bilaterally. The effect of the drug persisted for twenty-five days. Toxic manifestations were evident over a twenty-one day period.

It was noted throughout the series that a single large dose of 600 mg. produced less physiologic and definitely less toxic effects than total equivalent doses administered in portions of 100 mg. daily. This phenomenon was previously noted in animals by Link and his associates and attributed to imperfect intestinal absorption. The earliest toxic signs were most frequently noted to be lassitude and general malaise with aching in the costovertebral angles. Most interesting was the fact that, in spite of the extensive hemorrhages in practically all parts of the body, and especially subcutaneously, in no instance was the capillary fragility found to be increased (method of Wright and Lilienfeld).[16]

At present we are using smaller doses and are able practically to eliminate this risk. It seems important to include these reports, however, since they may serve to familiarize future users of this substance with the

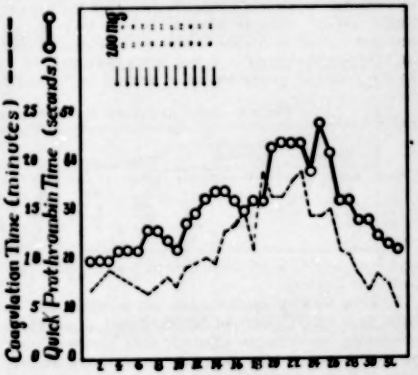

Chart 2 (case 6).—Response of coagulation and prothrombin times to administration of dicoumarin (total dose 2.2 Gm.). The patient, aged 60, weighing 127 pounds, had diabetes mellitus and arteriosclerotic endarteritis.

possible complications so that they may be recognized early and treated properly. The prothrombin time (Fullerton modification of the Quick technic)[17] was a rather good indication of the response of the patient to dicoumarin and the risk of hemorrhage. As can be seen from the figures in table 3, however, some patients had hemorrhages with prothrombin times which were much lower than those of others who never showed hemorrhagic manifestations. The use of a diluted plasma (25 per cent or 12.5 per cent) from animals as well as in man has resulted in greater sensitivity to variations in the prothrombin than undiluted plasma, thus reducing the risk of untoward reactions. The coagulation time (Lee-White two tube method)[18] was not found to be as reliable a guide but should be followed.

16. Wright, I. S., and Lilienfeld, Alfred: Pharmacologic and Therapeutic Properties of Crystalline Vitamin C (Cevitamic Acid), Arch. Int. Med. 57: 241 (Feb.) 1936.
17. Fullerton, H. W.: Estimation of Prothrombin: A Simplified Method, Lancet 2: 195 (Aug. 17) 1940.
18. Lee, R. I., and White, P. D.: A Clinical Study of the Coagulation Time of the Blood, Am. J. M. Sc. 145: 195 (April) 1913.

We examined various factors in an endeavor to determine a possible cause for this variability. Analysis of the clinical and laboratory studies on our patients revealed:

1. That the incidence of toxic reactions was not significantly influenced by age or sex.

2. That no significant correlation existed between malnutrition and frequency of toxic reactions. Nutritional status was estimated by weight-height tables, history and clinical impression and was good in all but 3 patients of whom none showed a hemorrhagic picture. There was no evidence of dehydration. The hematocrit studies, specific gravity of the plasma and serum proteins were within normal limits.

3. That no increase in capillary fragility (Wright-Lilienfeld method)[18] was detected even in the hemorrhagic cases. Seven patients presented an increased capillary fragility before taking dicoumarin. Only 2 of these showed hemorrhagic manifestations, but these showed no further increase in capillary fragility.

4. That the incidence of either hypochlorhydria or achlorhydria was not significantly greater in the hemorrhagic group. Gastric analysis in the toxic group revealed normal hydrochloric acid concentration curves in 4, hyperchlorhydria in 1 and hypochlorhydria in 3. In the nontoxic group we found normal hydrochloric acid curves in 6, hypochlorhydria in 3 and hyperchlorhydria in 2 cases.

5. That toxicity on the basis of retention due to renal dysfunction could not be established in our cases presenting hemorrhages although urea nitrogen, nonprotein nitrogen, urea clearance and urinary studies were carried out with this in mind.

6. That most of these patients were treated during the hot summer months and that Link [19] has observed that an abnormally high environmental temperature may enhance the action of dicoumarin in animals. We cannot make a definite conclusion regarding this factor at present.

7. The question as to whether liver damage acts as the mechanism by which the prothrombin is inactivated is still not definitely decided. Icteric index, bromsulphalein, cholesterol-ester ratio, Takata-Ara and total protein studies have been carried out on certain of our patients without demonstrating any conclusive liver damage as a result of the administration of dicoumarin. It was thought that more complete studies with large doses of vitamin K might throw further light on the fundamental mechanism involved in the action of this substance. Accordingly a potent synthetic vitamin K [20] was used to determine its effect on the hypoprothrombinemia and on the hemorrhagic manifestations produced by the oral administration of dicoumarin.[21] The synthetic vitamin K was administered parenterally, thereby eliminating the factor of variations in gastrointestinal absorption. Doses of 3.2 or 6.4 mg. of synthetic vitamin K were given twice daily to 8 patients in whom the prothrombin time was prolonged above 36 seconds. (Thirty-six seconds was arbitrarily selected, since it has been found that this represents an average potential or actual hemorrhagic level.) In each instance half the daily dose of synthetic vitamin K was given by the intramuscular and half by the intravenous route. Eight patients with comparable prothrombin times were used as controls. Administration of dicoumarin was discontinued for several days prior to the institution of synthetic vitamin K therapy. To 4 patients vitamin K substitute was administered immediately after the appearance of hemorrhage. In a fifth patient hemorrhagic manifestations developed eighteen hours after synthetic vitamin K therapy had been begun. The remaining 3 patients showed no bleeding tendency. Three patients in the control group showed bleeding while 5 were free from hemorrhage. Table 4 illustrates the effect of synthetic vitamin K on the hypoprothrombinemia produced by administration of dicoumarin. The dose of dicoumarin, duration of dicoumarin therapy and the dose of vitamin K substitute together with prothrombin times obtained during the course of vitamin K therapy are indicated. Similar data on 1 patient who received no synthetic vitamin K are included for comparison. In an interpretation of these curves it is important to bear in mind that withdrawal of dicoumarin of itself will be followed by a return of prothrombin time to normal over a period which varies with the dose of dicoumarin, duration of therapy and susceptibility of the patient. It should be emphasized that Andrus, Kark and Sauter,[22] using similar doses of vitamin K substitute, were able to restore prothrombin concentrations to normal within twenty-four to forty-eight hours in a series of patients with hypoprothrombinemia due to causes other than dicoumarin administration. Patients who failed to respond in twenty-four to forty-eight hours were termed vitamin K refractory. In the light of observations made by the aforementioned authors, the alteration in prothrombin time cannot be attributed to synthetic vitamin K in our patients. The time required for restoration of normal prothrombin levels in patients who received vitamin K substitute did not vary significantly from those noted in controls. Chart 5 graphically illustrates the absence of effect of the vitamin K substitute on the prolongation of prothrombin time in a typical case of dicoumarin induced hypoprothrombinemia.

Table 5 illustrates the effect of administration of the vitamin K substitute on hemorrhages complicating the hypoprothrombinemia produced by dicoumarin. Spontaneous bleeding associated with hypoprothrombinemia due to causes other than dicoumarin administration

TABLE 4.—*Effect of Vitamin K Substitute on Dicoumarin-Induced Hypoprothrombinemia*

	Dicoumarin		Vitamin K Substitute Mg. Every	Prothrombin Time (Seconds)											
Case	Mg./Kg.	Days	24 Hours	1 Day	2 Days	3 Days	4 Days	5 Days	6 Days	7 Days	8 Days	9 Days	10 Days	11 Days	12 Days	13 Days
11	15.5	4	6.4	44.8	49.2	54.0	51.0	46.6	44.5	38.2	35.8	29.0	29.6	27.4	....	....
13	29.5	9	6.4	47.6	50.8	48.8	58.3	37.2	31.6	28.4	22.0	....	....	....	....	....
7	39.4	18	12.8	44.6	41.8	46.2	41.0	41.4	45.4	36.6	28.0	28.4	27.4	....	....	....
20	32.5	5	None	42.2	47.3	40.0	....	42.3	36.0	31.3	29.5	20.7	....	....	....	....

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19. Link, K. P.: Personal communication to the authors.

20. The synthetic vitamin K used was Hykinone, produced by Abbott Laboratories.

21. Wright, I. S., and Prandoni, Andrew: The Dicoumarin 3,3'-Methylene-Bis-(4-Hydroxycoumarin): Its Pharmacological and Therapeutic Action in Man, presented before the American Society for Clinical Investigation, May 4, 1942.

22. Personal communication to the authors.

can be controlled by comparable doses of vitamin K substitute in from eight to twenty-four hours provided hepatic damage is not present. The data in this table show that despite adequate synthetic vitamin K therapy hemorrhages persisted for from four to nine days. In some instances hemorrhages required transfusion for control. No significant variations in the intensity or duration of hemorrhagic complications were observed between the patients who received vitamin K substitute and those who did not.

Chart 6 demonstrates the absence of a prophylactic effect of administration of synthetic vitamin K on the hemorrhagic tendency, which occasionally occurs with dicoumarin induced hypoprothrombinemia. This patient received 12.8 mg. of vitamin K substitute for forty-eight hours prior to the development of hemorrhage, despite which he bled profusely. Because of the severity of the hemorrhage, a transfusion with 6 day old bank blood was given on the sixth day. Hemorrhage was finally controlled on the ninth day, as previously mentioned. It was later found that bank blood more than 72 hours old is ineffectual in the treatment of this condition. The foregoing data indicate that the hypoprothrombinemia and bleeding induced by the administration of dicoumarin is refractory to this therapy with synthetic vitamin K given in doses which are greater than those which control hypoprothrombinemia from other causes. The evidence does not warrant the conclusion, however, that this failure in response to synthetic vitamin K is on the basis of hepatic damage similar to that produced by chloroform and phosphorus. Hypoprothrombinemia of the degree by dicoumarin administration in this series, if due to liver damage, would represent decided destruction of hepatic parenchyma. Destruction of this magnitude is probably incompatible with recovery over the brief period required for restoration of prothrombin time to normal following dicoumarin withdrawal, and especially the rapid restoration following fresh blood transfusions.

Bingham, Meyer and Pohle [14] presented further evidence against the action of dicoumarin being based on severe liver damage. Even when their dogs were given fatal doses there were no gross or microscopic lesions which could be attributed to the substance administered. They hypothesized the possibilities that the formation of prothrombin in the liver is physiologically inhibited and the latent period (twenty-four hours or more) before a detectable change is noticed in the prothrombin time may represent a period necessary for the using up of the prothrombin available in the blood. Other reservoirs about which little is known may also be drained during this period. Additional possibilities may be suggested but thus far are not proved. The latent phase may be due to the need for dicoumarin to undergo certain changes before it is capable of acting, or a protective mechanism may be promptly set up which temporarily inhibits the action of dicoumarin against prothrombin but later fails to continue this protection. The prothrombin produced or liberated into the blood stream may later be inactivated by dicoumarin, which it appears may also inactivate both the vitamin K present in the body and any additional synthetic vitamin K taken while the dicoumarin is present. The knowledge regarding the mechanism by which dicoumarin acts is thus seen to be relatively limited, although new and interesting conditions are constantly being discovered.

THE THERAPEUTIC VALUE

The therapeutic value of this dicoumarin has not yet been clearly established. Because of its obvious theoretical value as a valuable adjunct in an anticoagulant therapy, several groups of workers have attempted the difficult task of evaluating it. Our own efforts during the first year of study of its use in man have been concentrated on studying the mechanism, the untoward effects, the treatment of these untoward effects and the determination of a safe but pharmacologically active dosage. We have administered this drug to 40 patients who have been carefully followed as to prothrombin time, coagulation time, bleeding time, capillary fragility, evidences of hemorrhage, tests for kidney and liver function and blood counts. Additional studies have been carried out in some. We cannot draw conclusions from this small group but will present certain facts and experiences which may be of value to others undertaking to use this substance. Unfortunate complications may thus be minimized.

One of the most interesting groups of patients for study with this anticoagulant falls in the general category of thrombophlebitis. We have used it on

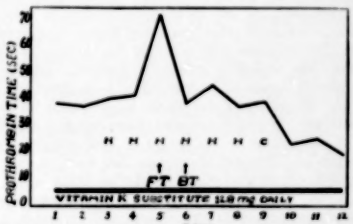

Chart 6 (case 5).—Response of prothrombin time to 36.4 mg. of dicoumarin per kilogram in eighteen days. *H* indicates hemorrhage; *C*, cessation of hemorrhage; *T*, transfusion; *B*, bank blood; *F*, fresh blood.

10 such patients who have been carefully followed. In our studies dicoumarin was administered only by mouth. In order to determine the size and frequency of the dose of dicoumarin necessary to obtain the desired effects and still avoid untoward complications, it is advisable to carry out daily prothrombin and coagulation determinations. As previously stated, wide variations in susceptibility to dicoumarin have been observed in different patients. Unfortunately we have as yet been unable to identify the cause of this phenomenon. The time required for the initial effect to manifest itself is a poor guide in estimating susceptibility unless prothrombin time estimations are performed on diluted plasma. Twenty-five per cent diluted plasma renders possible the detection of slight fluctuations in prothrombin concentration which escape observation if undiluted plasma is used. In order to secure an unequivocal end point, dilutions should be made with a saline solution of fibrinogen 600 mg. per hundred cubic centimeters. The variations in diluted plasma prothrombin time and the duration of the latent period serve as a fairly satisfactory but not infallible guide to planning a dosage schedule. On the basis of observations that single doses give rise to alterations in the prothrombin time which can be represented by parabolic curves, we have attempted to maintain fairly constant prolongation of prothrombin time by administering an effective dose and

varying the interval, so that a succession of peak effects is obtained. We thus attempted to maintain the prothrombin time at the level desired with minor fluctuations. While this is usually possible, the prothrombin time frequently becomes so prolonged that a longer period between doses becomes necessary.

The majority of the patients in this series received 300 mg. after breakfast daily the first two or three days. Subsequent doses were administered at two to three day intervals, depending on the degree of prothrombin time prolongation obtained with 25 per cent diluted plasma. The levels between which we have attempted to maintain prothrombin times are 30 to 35 seconds for undiluted plasma and 70 to 90 seconds for 25 per cent diluted plasma. Hence when prothrombin time falls below 30/70 a dose is indicated. If, however, the prothrombin time exceeds 35/90, dicoumarin is withheld.

Occasionally the prothrombin time may fall rapidly and attain normal levels before the effect of subsequent doses is noted. In such instances we have experimentally attempted to enhance dicoumarin absorption by simultaneous administration of sodium bicarbonate in 1 Gm. doses. This was done on the basis of the knowledge that, as the dicoumarin is soluble only in an alkaline medium, absorption and hence the pharmacologic characteristic effects might be hastened. This procedure has met with little or no success. The usual latent period seems to be inevitable, as pointed out by Bingham, Meyer and Pohle on the basis of their intravenous studies. We have not used doses calculated on the basis of milligrams per kilogram of body weight since the factor of intestinal absorption has been shown to be variable. It is also much simpler to utilize a standard capsule. As many as needed may be administered. Of the ten patients 8 showed prompt and uncomplicated recovery, with subsidence of clinical evidence of activity of the process within three to ten days.

Two patients, both suffering from recurrent migratory thrombophlebitis, suffered relapses when the prothrombin time returned to normal levels after dicoumarin therapy. In 1 instance (E. S.) relapse consisted of a brief episode of redness and tenderness of a previously involved left saphenous vein with tachycardia and increased sedimentation rate, when in the course of the therapy the prothrombin time was permitted to drop to 25 seconds (54 seconds with dilution to 25 per cent). Increased dosage with further prolongation of the prothrombin time was accompanied by recovery with no further complications. Results in the other patient (J. T.), also suffering from recurrent migratory thrombophlebitis, must be considered as unsuccessful from the point of view of dicoumarin therapy:

J. T., admitted to the New York Post-Graduate Hospital on Sept. 20, 1941, had phlebitis involving several areas of the saphenous veins of both legs. With rest in bed and small doses of sulfadiazine the activity had subsided by October 10. Dicoumarin was administered in 300 mg. doses on the first, second, third, fourth, seventh, eighth, twelfth and thirteenth days, a total of 2.4 Gm. (45.9 milligrams per kilogram), maintaining the prothrombin time between 26 and 46 seconds and the coagulation time between 7 and 12 minutes. By October 30 the phlebitis had apparently subsided and by November 8 the sedimentation rate, which during activity had reached 41, had subsided to a normal level of 9 (Westegren method). On December 10 he had a recurrence and on December 12 dicoumarin was started. This time he received the following dosage: 300 mg. on the first, second, fourth, sixth, tenth, twelfth, sixteenth, nineteenth, twenty-second and twenty-sixth days, a total of 3 Gm. (57.6 milligrams per kilogram). By December 17 his phlebitis had subsided but on December 22, while his prothrombin time was 37 seconds, two new areas of thrombophlebitis developed. (This is the only time we have seen this occur with a considerably prolonged prothrombin time due to dicoumarin.) The dicoumarin was continued and the phlebitis had subsided by Jan. 3, 1942, at which time the drug was discontinued. On February 9 another episode of active thrombophlebitis occurred and dicoumarin was started February 11. This time he received 300 mg. of dicoumarin on the first, second, fourth, seventh, eighth, ninth, eleventh, fourteenth, sixteenth, twenty-first, twenty-second and twenty-third days, a total of 3.6 Gm. (69.2 milligrams per kilogram). Improvement followed the administration of the substance and the patient was allowed out of bed on March 3. On March 10, when the prothrombin time was 26 seconds (60 seconds with 25 per cent diluted plasma), an acute depressive state developed and the patient had to be transferred to the Bellevue psychiatric wards.

We must conclude, therefore, that in spite of large doses of dicoumarin we could not prevent the recurrence and progression of the migratory thrombophlebitis in this instance.

The other patients, including 2 with recurring migratory thrombophlebitis, were apparently helped by dicoumarin, although we cannot draw any further conclusions regarding its therapeutic value in so small a series of such an unpredictable disease. This series will be enlarged during the next year. It has seemed wise to present the histories given briefly in order that new workers may appreciate some of the problems involved.

We shall now summarize briefly some of the interesting results of the laboratory studies which have been carried out on these and other patients. In 15 cases in which hematocrit readings were followed they were found to be within the normal range before and during the administration of dicoumarin. In 15 cases in which the bleeding time (Ivy method) was followed a considerable variation in response to dicoumarin was noted. All but 1 patient showed some prolongation, but this varied from a very slight prolongation as from 2 minutes 30 seconds to 3 minutes 15 seconds to a definite prolongation as from 2 minutes 30 seconds to 10 minutes 35 seconds. The extent of the increase in bleeding time bore no direct relationship to the extent of increase in the prothrombin time in different patients, although the general trend was parallel. In a single case the peak in prothrombin time frequently but not always coincided with the peak in bleeding time. Clot retraction studies have been carried out in 12 cases with the McFarlane technic. The normal standard is 38 to 50 per cent. The changes encountered as a result of administering dicoumarin may best be presented by listing the ranges encountered. C. L., 48 to 21 per cent; E. S., 44 to 32.1 per cent; I. P., 43.8 to 21 per cent; S. M., 44 to 30 per cent; D. S., 46 to 33 per cent; S. F., 34 to 28 per cent; A. L., 42 to 38 per cent; M. G., 56 to 26 per cent; H. B., 46 to 38 per cent; J. T., 59 to 21 per cent; D. L., 42 to 28 per cent; F. T., 44 to 21 per cent. In most instances maximum clot retraction changes coincided with maximum prothrombin time changes but in the case of E. S. and of F. T. this was not so. The following liver function tests have been performed on all of our patients before and during dicoumarin therapy: bromsulphalein, icteric index, cholesterol-ester ratio and plasma proteins. In addition,

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when further data were desired the Takata-Ara test was performed. In our entire series of 40 patients we have failed to find any evidence of liver damage as indicated by these tests. This, as pointed out, is of especial interest and significance in the use of dicoumarin. The renal function has been checked before and during dicoumarin therapy with the urea clearance and the Mosenthal two hour urinary function test. In several instances the urea nitrogen-nonprotein nitrogen ratio was determined. All but 3 patients showed normal renal concentrating capacity on the basis of the two hour Mosenthal test. Other tests of the renal function on these patients failed to reveal any evidence of renal damage. Platelet counts were followed during treatment of 15 patients with no deviation from the normal range in any instance. As previously mentioned, one of the most interesting findings was the total lack of consistent change in the capillary fragility as determined by the positive pressure method (Wright and Lilienfeld). Even in the cases in which extensive ecchymosis and bleeding develops slight variations occurred which were unrelated to prothrombin or coagulation times or any other findings. Observations were made in all 40 cases. This is directly contrary to the findings in frank scurvy, in which bleeding and ecchymosis are almost invariably accompanied by increased capillary fragility as determined by this method.

The influence of the dicoumarin on the suspension stability of the blood as manifested by the sedimentation rate was of interest. In our experience the administration of dicoumarin per se was not accompanied by an increased sedimentation rate (Westergren method). Variations consistent with the pathologic state occurred in patients suffering from phlebitis, infection or a hemorrhagic state produced by dicoumarin. In other words, prolongation of the prothrombin time and clotting time due to dicoumarin administration unaccompanied by any of the aforementioned complicating factors was not accompanied by an increased sedimentation rate. In addition to the patients with thrombophlebitis the remaining patients in our series were suffering from arteriosclerosis obliterans or thromboangiitis obliterans. Again we were dealing with diseases which are chronic and in many instances unpredictable as to course. We have quite consistently noted an increased tendency to bleed at the site of ulceration or gangrene. This may be explained by the findings of Bingham, Meyer and Pohle [14] of the significant dilatation of the minute vessels of dogs who received dicoumarin whether they died from this substance or were killed for the study. We cannot, however, at this time arrive at any definite conclusions as to whether this increased bleeding is actually accompanied by an accelerated rate of healing. We have as yet seen no additional evidence of therapeutic value of dicoumarin in these diseases.

COMMENT

An attempt has been made to present briefly the historical and experimental background which led to the use of dicoumarin in man. Problems regarding the mechanism of the action of dicoumarin have been discussed. The results of studies of the effect of this substance on the prothrombin time, coagulation time, bleeding time, clot retraction, sedimentation rate, liver function, renal function, capillary fragility, blood count, response to therapy with vitamins C, P and K and other factors have been presented.

The complications which may be encountered in the use of dicoumarin and the treatment of these complications have been described. The therapeutic discussion has been limited to a consideration of dosage and to the effect of this substance on patients suffering with thrombophlebitis, thromboangiitis obliterans and arteriosclerosis obliterans. The first year and a half of this study was for the most part devoted to the mechanism and pharmacologic action of dicoumarin in man. It is expected that therapeutic considerations will occupy a more prominent part in future studies.

400 Madison Avenue.

THE EFFECTS OF EXPERIMENTAL ADMINISTRATION OF DICOUMARIN

3,3'-METHYLENE-BIS-(4-HYDROXYCOUMARIN)

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AND
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The identification and synthesis of the hemorrhagic agent of hemorrhagic sweet clover disease, dicoumarin [3,3'-methylene-bis-(4-hydroxycoumarin)], by Link and his associates [1] have provided a pure substance which can be administered to animals and man and cause a considerable diminution of the prothrombin content of the blood. Their paper carried also the obvious suggestion that this compound might be of value in clinical conditions when interference with the coagulability and prothrombin content of blood was desirable. Since the most probable use of this substance in clinical medicine is in the prevention of thrombosis, its value in such conditions can be determined only by clinical trial. However, several questions should be answered by experiments with animals: First, does the lowering of the prothrombin content of the blood by this drug prevent or delay experimental thrombosis? Second, can the drug be given in amounts sufficient to produce the desired effects without producing untoward reactions? Third, can the effects of the drug be controlled? Fourth, what factors alter the effectiveness of this drug? Satisfactory answers to some of these questions have been given in reports by Link and his associates,[2] by Butt, Allen and Bollman [3] and by Bingham, Meyer and Pohle.[4]

In this report we wish to add further data which indicate that certain experimental forms of thrombosis may be prevented or delayed by the administration of dicoumarin. Additional studies substantiate the follow-

From the Division of Experimental Medicine, the Mayo Foundation.
Read before the joint meeting of the Section on Practice of Medicine and the Section on Experimental Medicine and Therapeutics at the Ninety-Third Annual Session of the American Medical Association, Atlantic City, N. J., June 12, 1942.

1. Stahmann, M. A.; Huebner, C. F., and Link, K. P.: Studies on the Hemorrhagic Sweet Clover Disease: V. Identification and Synthesis of the Hemorrhagic Agent, J. Biol. Chem. **138**: 513-527 (April) 1941.
2. Overman, R. S.; Stahmann, M. A.; Sullivan, W. R.; Huebner, C. F.; Campbell, H. A., and Link, K. P.: Studies on the Hemorrhagic Sweet Clover Disease: VII. The Effect of 3,3'-Methylene-Bis-(4-Hydroxycoumarin) on the Prothrombin Time of the Plasma of Various Animals, J. Biol. Chem. **142**: 941-955 (Feb.) 1942.
3. Butt, H. R.; Allen, E. V., and Bollman, J. L.: A Preparation from Spoiled Sweet Clover [3,3'-Methylene-Bis-(4-Hydroxycoumarin)] Which Prolongs Coagulation and Prothrombin Time of the Blood: Preliminary Report of Experimental and Clinical Studies, Proc. Staff Meet., Mayo Clin. **16**: 388-395 (June 18) 1941.
4. Bingham, J. B.; Meyer, O. O., and Pohle, F. J.: Studies on Hemorrhagic Agent 3,3'-Methylene-Bis-(4-Hydroxycoumarin): I. Its Effect on the Prothrombin and Coagulation Time of the Blood of Dogs and Humans, Am. J. M. Sc. **202**: 563-578 (Oct.) 1941.

ing statements: The effect of the drug in reducing the prothrombin of the blood is uniform in dogs, and the amount of change is, within limits, proportional to the amount administered. Similar effects are produced when administration of the drug is repeated. Excessive amounts do not produce gross or microscopic evidence of injury to any specific tissue, and the animals appear normal when the administration of the drug has been discontinued. Excessive bleeding does not occur when operation is performed on dicoumarinized animals except in those which have been given excessive amounts for prolonged periods. The prothrombin time of the blood of dicoumarinized dogs and the bleeding tendency may be reduced by transfusions of fresh whole blood. Dogs receiving large amounts of sulfathiazole react in normal manner to dicoumarin. We should emphasize that inanition or experimental hepatic or renal damage produced in dogs greatly increases the effectiveness of dicoumarin and that due caution should be exercised in administering this drug to patients in the presence of any of these defects.

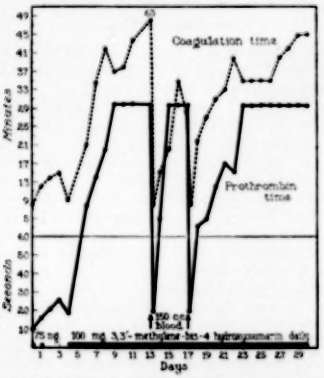

Chart 1.—The effect of oral administration of dicoumarin on the coagulation time and prothrombin time (dog). At the time of the first transfusion the dog had been bleeding from a slight abrasion for three days and was extremely anemic. The bleeding stopped a few minutes after transfusion. At the time of the second transfusion slow bleeding from a venipuncture wound had continued for two days. Bleeding ceased a few minutes after transfusion.

EXPERIMENTAL PROCEDURE

It was found that a definite decrease of the prothrombin content of the blood of dogs could be maintained after forty-eight hours by daily administration of dicoumarin [5] in amounts equivalent to 1 mg. for each kilogram of body weight, the material being equally effective as the dry powder by mouth or injected intravenously as an alkaline solution. By daily administration of small amounts of this drug the prothrombin time of the blood could be maintained at approximately two or three times the normal value of 10 seconds (dogs) for at least six weeks, with no other apparent change in the condition of the animal.

The prothrombin content of the blood was determined by a slight modification of Quick's method. Nine volumes of blood were added immediately to one volume of 1.34 per cent solution of sodium oxalate. After centrifugation 0.1 cc. of this plasma was added to 0.1 cc. of Quick's acetone washed rabbit brain thromboplastin and the mixture placed in a water bath at 37 C. for five minutes. The prothrombin time was taken as the time required for coagulation after addition of 0.1 cc. of 1.11 per cent solution of calcium chloride. With normal canine blood the prothrombin time was usually 9 to 10 seconds, the duplicate determinations checking within 1 second. When longer times are required, a wider variation is found in duplicate determinations, but since with undiluted plasma such times represent only a small percentage of the normal amount of prothrombin, such differences are insignificant in these experiments. Prothrombin times of less than 30 seconds were checked further by dilution of the plasma to 50, 25 and 12.5 per cent of its concentration with saline solution.

The coagulation time was determined at room temperature after blood had been taken by venipuncture in a saline washed syringe. The blood was placed immediately in a small tube which was inverted every thirty seconds after five minutes and every minute after ten minutes. In these studies no appreciable change of coagulation time was found unless the prothrombin time of the blood was prolonged more than five seconds beyond the normal value. When extremely small amounts of prothrombin were present, coagulation time was usually much delayed, roughly in proportion to the loss of prothrombin.

No definite gross or microscopic pathologic change of any organs was found after administration of large amounts of dicoumarin. Twenty-four to forty-eight hours after the oral or intravenous administration of 100 mg. for each kilogram of body weight there was widespread dilatation of the small blood vessels of the liver with noticeable filling of all blood sinusoids of the liver. The hepatic cells did not appear abnormal but some of the stellate cells had engulfed some lipoid staining material. The results of dye retention tests for liver function had been within normal limits, and there was no retention of bile pigment. Necropsy was performed also on other dogs which had received 10 to 20 mg. daily for six weeks and to which repeated transfusions had been given to prevent fatal hemorrhage. Such animals usually showed petechial hemorrhagic regions in all organs, especially in the liver, kidneys and spleen, but there were no changes that could not be attributed entirely to the hemorrhage. These changes had disappeared entirely in other dogs similarly treated but allowed to recover for two weeks after discontinuation of the drug.

Our observations are in conformity with those of Link that the hemorrhagic condition characteristic of the sweet clover disease does not appear unless dicoumarin is fed or injected continuously over a period of time. The development of the hemorrhagic condition is more than a function of time, since animals may be maintained for several weeks with a prothrombin time two to three times elevated by intermittent administration of the drug and without any untoward effects being apparent. With larger amounts of the drug daily administered the prothrombin time is elevated further and the hemorrhagic condition appears in from ten to twenty days with no further change of the coagulation time or the prothrombin time. Apparently some additional factor is necessary for the development of the hemor-

5. Obtained through Dr. J. F. Biehn of Abbott Laboratories.

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rhagic condition. The imminent development of the hemorrhagic condition in dogs usually is detected by the appearance of continuous bleeding from a venipuncture wound two or three days prior to death from the hemorrhagic condition. Transfusion of fresh whole blood at this time stops the bleeding from venipuncture wounds in a few minutes (chart 1). The coagulation time and prothrombin time of the blood return toward normal. Extensive surgical procedures have been carried out in dicoumarinized dogs that had greatly altered prothrombin content of the blood at various times before the development of the hemorrhagic condition. The bleeding occasioned by the surgical procedures has been surprisingly small, not materially greater than that which would obtain in normal dogs, and in great contrast to the bleeding which occurs in dogs that have prolonged coagulation time due to heparin.

The response of individual dogs to a single intravenous injection of 10 mg. of dicoumarin for each kilogram of body weight was found to be fairly uniform. The plasma prothrombin fell to about 15 per cent of normal within three days and returned to normal within eight days. An increase of prothrombin time was apparent within twenty-four hours and the prothrombin time increased by the third day to about 90 seconds (normal 10 seconds). Some decline was apparent on the fourth day and almost normal values were observed by the sixth day. There was little alteration of the coagulation time of the blood during this period. The results of tests for heparin in the blood, by neutralization with protamine, were entirely negative. The intravenous injection of heparin at any time did not alter the prothrombin content of the blood, although it definitely delayed coagulation time during its period of activity. The rate of disappearance of injected heparin from the blood and its effectiveness in delaying coagulation were not materially different in dicoumarinized dogs and in normal animals. Apparently the rapid elimination of heparin from the blood was the limiting factor in these experiments.

Renal damage was produced in 4 dogs by the subcutaneous injection of uranium acetate (20 to 30 mg. for each kilogram of body weight in divided doses) at various times after they had received 10 mg. of the dicoumarin compound for each kilogram of body weight. In these dogs the prothrombin of the blood was subsequently reduced to less than 6 per cent of normal and the prothrombin time increased beyond 120 seconds. The prothrombin content of the blood remained depressed for eight, thirteen, fourteen and fifteen days respectively. Total anuria was produced in 2 additional dogs, in 1 by bilateral nephrectomy and in the other by bilateral ligation of the ureters, two days after they had received a similar amount of the drug. In both cases the prothrombin fell to less than 5 per cent of the normal value within forty-eight hours and the prothrombin times were 150 and 195 seconds. Both dogs died on the third postoperative day with extensive hemorrhage into their peritoneal cavities. We were unsuccessful in our attempts to produce anuria in dogs during the period of dicoumarinization by oral administration of large amounts of sulfathiazole, and the changes of the blood prothrombin were similar to those expected from the dicoumarin. The greatly increased activity of dicoumarin during periods of renal damage is striking (chart 2). In view of the facts reported by Link and his associates that they were unable to detect dicoumarin in the urine of dogs after administration of large amounts, it may be suggested that the kidney plays an important role in the destruction of this compound.

A mild degree of hepatic damage was produced in dogs which were exposed to carbon tetrachloride vapor for thirty minutes each day. This amount of exposure produced slight bilirubinemia but did not lower the prothrombin content of the blood. Administration of the dicoumarin compound, 10 mg. for each kilogram of body weight, reduced the prothrombin content of the blood more and for periods of days three to five times longer than similar amounts of dicoumarin before exposure of the same animal to carbon tetrachloride.

Animals fasting for seven days or longer were likewise more susceptible to the effects of dicoumarin. Animals that received vitamin K_1, 2 to 5 mg. daily during fasting, usually responded like normal animals when dicoumarin was given. When vitamin K_1 was given to fasting dogs two or three days after dicoumarin had been given, the effect was less pronounced than the

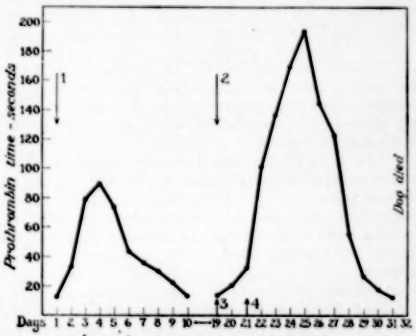

Chart 2.—The effects of renal injury after administration of dicoumarin on the prothrombin time of the blood. The first curve is typical for the response of a normal dog and the second curve shows the exaggerated response due to renal injury. This response was much greater in animals after bilateral nephrectomy or ligation of both ureters.

effects of food. Animals fed two or three days after fasting and administration of dicoumarin showed a return of their plasma prothrombin to normal within twenty-four hours.

Murry and Janes[6] found that heparin must be injected in amounts sufficient to keep the coagulation time of the blood greater than 13 minutes in order to prevent thrombosis of glass cannulas placed in the carotid arteries of dogs. When heparin was not given to control dogs the cannulas thrombosed in about twenty minutes, but they remained patent for more than twenty-four hours in the heparinized dogs. We performed similar experiments by placing glass cannulas in the carotid and femoral arteries of normal and dicoumarinized dogs. In the dicoumarinized dogs in which the prothrombin time was elevated beyond 30 seconds, the cannulas remained patent for six to eight

6. Murry, Gordon, and Janes, J. M.: Prevention of Acute Failure of Circulation Following Injury to Large Arteries: Experiments with Glass Cannulas Kept Patent by Administration of Heparin, Brit. M. J. 2:16-7 (July 6) 1940.

hours, when the experiments were terminated. Our control series was similar to that of Murry and Janes except that an occasional cannula would remain patent for several hours.

Other experiments were performed in which blood was clamped in portions of the jugular and femoral veins with soft clamps. This blood did not clot in normal dogs for several hours, but it was found that fresh blood injected by syringe into the occluded vein clotted within a few minutes. When this clot was allowed to be washed out by removal of the clamps and the blood was allowed to flow through the veins for fifteen minutes, subsequent blood held in the same veins by clamps clotted within ten minutes. The clot could be washed out again and the process repeated many times. Similar procedures in dicoumarinized dogs with prothrombin times greater than 30 seconds showed definite evidence of delayed thrombosis in the occluded veins. Normal blood injected into the occluded veins coagulated in a few minutes, but when this clot was washed out for a few minutes subsequent occlusion of the veins did not cause the animal's own blood to clot at any time in less than thirty minutes and usually no clot was found after several hours. When coagulation did occur in the veins of the dicoumarinized animals the clot was softer and more friable than in the normal animals. After the dicoumarin clot had been washed out of the vein, coagulation was no more rapid in subsequent occlusions.

We have used dicoumarin to replace heparin in many experiments in the physiologic laboratory. Cannulas of glass or metal which rapidly thrombose in the blood vessels of normal dogs have been maintained patent in dicoumarinized dogs during the course of experiments lasting six to eight hours. The procedure that we have found satisfactory is to give orally 10 mg. of the drug for each kilogram of body weight on the first day and 5 mg. per kilogram on each subsequent day. After the third day the prothrombin time of the blood is 30 to 45 seconds or more, and we have always used such animals for the experiments before the seventh day.

SUMMARY

Studies which have shown that dicoumarin prolongs the prothrombin and the coagulation time in animals have been confirmed by studies on dogs. No harmful effects during or after the administration of this compound were found in dogs which were maintained for six weeks with prothrombin times two to three times normal. Continuous administration of excessive amounts of this compound produces in dogs a condition similar to that found in the hemorrhagic sweet clover disease. The prothrombin time of the blood and the bleeding tendency may be partly controlled by transfusion of fresh whole blood. Vitamin K deficiency, inanition or hepatic or renal injury greatly exaggerates the effect of this drug. The administration of large amounts of sulfathiazole does not alter the effectiveness of the dicoumarin compound. The action of heparin is not prolonged when given to dicoumarinized animals and heparin is not involved in the action of dicoumarin.

The tendency toward thrombosis, as demonstrated experimentally by the thrombosis of glass or metal cannulas interposed in arteries or by thrombosis in occluded veins, is greatly reduced in animals that have prolonged prothrombin times due to the administration of this drug.

ABSTRACT OF DISCUSSION

ON PAPERS OF DRS. ALLEN, BARKER AND WAUGH, DRS. WRIGHT AND PRANDONI AND DRS. BOLLMAN AND PRESTON

DR. SHEPARD SHAPIRO, New York: This in vivo anticoagulant dicumarol is to the investigator and the clinician a new instrument. It might aid in the further elucidation of the mechanism of blood clotting; it might help in the further determination of the chemical nature of prothrombin. It may be utilized in operative procedures in which it is required that the blood be maintained in a noncoagulable state. The evidence presented here today, and that presented by other workers, has shown that dicumarol may be used therapeutically when anticoagulant effects are desired. Because of the latent period between administration and detectable response, it is not applicable when immediate action is sought. It should be realized that the administration of an anticoagulant involves an element of risk by reason of the interference with a fundamental property of the blood; namely, clotting. Dicumarol is an in vivo anticoagulant by virtue of its selective toxic action, whereby it interferes with the elaboration of prothrombin. Its use as a therapeutic agent already implies the presence in the patient of a disturbed state as a result of the existing disease. Hence the tolerance observed in normal persons may prove to be an unreliable guide in such cases. It is therefore necessary, as emphasized by Dr. Allen and his co-workers, to individualize the dosage level by frequent estimations of the prothrombin times. Drs. Sherwin, Redish, Campbell and myself have found it necessary to increase the sensitivity of the prothrombin estimations. Using the technic as described by Prof. Karl Paul Link and his students, the prothrombin times of whole and diluted plasma are estimated at the same time. We strongly recommend the prothrombin estimation of 12.5 per cent, as well as whole plasma, as a guide to dosage. We have found that it is safe for therapeutic purposes to give a quantity of dicumarol which will result in a prolongation of the prothrombin time of the diluted (12.5 per cent) plasma to between twice and three times the normal figure while that of the whole plasma is maintained at less than double the normal value. By observing this rule, it has been possible to give dicumarol intermittently for months without difficulty. It is interesting that, when fed during the menstrual period, this substance has not significantly altered this function.

DR. K. K. CHEN, Indianapolis: These contributions constitute the beginning of the last chapter of this subject, completing the logical sequence of introduction of any new drug if the therapeutic values can be finally established. Through the arrangement of the Wisconsin Alumni Research Foundation, the product has been placed in several medical centers for experimental investigation. As Dr. Shapiro announced, the word dicumarol has been adopted by the foundation, and, no doubt, will be submitted to the government and the Council on Pharmacy and Chemistry for final approval. Much of the toxicologic work has been presented by Dr. Meyer of Wisconsin. Many additions have been made by Dr. Bollman. During the last year it has been my privilege to study the effects of dicumarol in a large number of animals. Dicumarol may cause two types of deaths: the acute and the subacute. If a single dose of dicumarol of from 60 to 80 mg. per kilogram is injected intravenously, or one of 500 to 700 mg. per kilogram is given by mouth, the animals gradually develop elevation of rectal temperature and clonic convulsions and die within a few hours from circulatory collapse. The prothrombin time in those animals is not altered, and naturally no bleeding can be demonstrated at postmortem examination. If dicumarol is repeatedly administered, a different picture results. In rabbits an intravenous injection of 1 mg. per kilogram daily will invariably cause death, and in dogs daily doses of 5 mg. per kilogram uniformly produce death. In mice and rats the feeding of 0.01 per cent of dicumarol in food is uniformly fatal. Please note that these are small doses, given repeatedly. Those animals, of course, have very great prolongation of their prothrombin time, and death usually occurs within ten to thirty days. At postmortem they will show hemorrhages in various tissues and organs. Pulmonary edema is frequently encountered

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and secondary anemia is certainly obvious. In rats we have observed in almost 50 per cent of the cases central necrosis of the liver, and we have also observed occasionally central necrosis of the liver in mice, rabbits and rats. These data clearly indicate that dicumarol is a drug of high potency and also of high toxicity. My experiments were conducted under the most severe conditions and these results should not be used as arguments against careful clinical trials. It is possible that if these doses were reduced they would be perfectly harmless to these animals. Nevertheless the drug must be given by certain criteria, such as the determination of the prothrombin time or other appropriate tests. Otherwise unfortunate accidents may arise.

CLINICAL EXPERIENCES WITH DICOUMARIN

3,3'-METHYLENE-BIS-(4-HYDROXYCOUMARIN)

WINFIELD L. BUTSCH, M.D.
AND
JOHN D. STEWART, M.D.
BUFFALO

The dicoumarin compound [3,3'-methylene-bis-(4-hydroxycoumarin)] is a white, crystalline, insoluble powder. The brilliant work of Campbell and Link [1] resulted in its preparation and identification as the hemorrhagic agent causing the death of cattle eating spoiled sweet clover. Butt, Allen and Bollman [2] first reported its clinical use in prolonging the prothrombin and clotting times of the blood. The response of 150 patients to the administration of this drug forms the subject of this report.

DOSAGE

The dose employed varied in size from 300 mg. the first day followed by 200 mg. the second day up to a 300 mg. dose for three successive days, given orally. In chart 1 is represented graphically the effect of the smallest dose used contrasted with the largest dose used. The prothrombin time was determined by the method of Quick.[3] The clotting time of the blood is elevated similarly to the prothrombin time. The larger dose produced a prothrombin time of more than 180 seconds at one time or another in half of the patients to whom it was given. However, the clotting time by the method of Lee and White [4] rarely rose above 25 minutes. Certainly this larger dose produces a sufficient response as to both extent and duration. The smaller dose did not cause a sufficiently consistent effect.

In chart 2 is represented graphically two doses of intermediate size. These did not produce the decided increase of the prothrombin time except on a rare occasion. The dose of 300 mg. on two successive days was sufficient to prolong the prothrombin time and coagulation time in nearly every instance. We believe that it should be used as the basic dose for routine use. In the occasional case blood determinations may show that an additional 300 mg. is advisable. Twenty-four to forty-eight hours are required for the effect to become apparent in the blood following oral administration. Usually it is forty-eight hours.

Two hundred mg. on two successive days proved to be a satisfactory dose for children. Unpleasant or deleterious side effects were not noted, with the exception of bleeding phenomena to be noted later.

INDICATIONS

We have been especially interested in the use of this drug as a prophylactic measure against postoperative thromboses and embolism. With a few exceptions the patients comprising this series have had the drug administered the day after an operation. Some have even had it given two days before an operation. In the 130 patients who received this drug and were operated on wound healing took place in the normal manner, with 3 exceptions—small hematomas developed in 2 and the third had a large hematoma that required operative evacuation of the clot and ligation of a bleeding vessel.

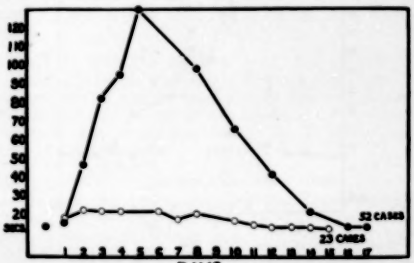

Chart 1.—Effect of dicoumarin on prothrombin time (normal equals 16 seconds). Curve marked off by black circles produced with 300 mg. dose given orally daily for first three days; curve marked off by white circles produced with smaller dose (200 mg. for first two days).

Two patients with clinical pulmonary embolism and hemoptysis were later given dicoumarin. The hemoptysis was not aggravated and further embolic phenomena did not occur.

Six patients with thrombophlebitis of the long saphenous or femoral veins were treated with dicoumarin compound. In five days the tenderness had disappeared and the swelling had subsided. The patients were then urged to walk about with elastic bandages on the affected extremity. Two patients had a recurrence of the thrombophlebitis, one in the same leg and the other in the arm. The recurrence took place two weeks after the drug was administered, which coincides with the time that the drug effect disappears. At the present time we are administering the drug in at least weekly intervals in order to maintain its effect for at least four weeks.

We have not had occasion to use this drug in combination with the sulfonamides in certain infections but believe that it is deserving of trial.

The use of dicoumarin compound in 2 cases of threatened gangrene of the leg due to arteriosclerosis obliterans did not prevent the occurrence of the gangrene.

The clinical course of rheumatoid arthritis was not altered after six weeks of dicoumarin therapy.

Dr. J. F. Biehn cooperated in this work, and the Abbott Laboratories supplied the dicoumarin that was used.

From the Department of Surgery, University of Buffalo School of Medicine, and the Surgical Service of the Edward J. Meyer Memorial Hospital.

Read before the Section on Pathology and Physiology at the Ninety-Third Annual Session of the American Medical Association, Atlantic City, N. J., June 11, 1942.

1. Campbell, H. A., and Link, K. P.: Hemorrhagic Sweet Clover Disease: Isolation and Crystallization of Hemorrhagic Agent, J. Biol. Chem. **138**: 21-33 (March) 1941.

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CONTRAINDICATIONS

Dicoumarin should be used with caution or not at all in cases in which ulcerating or granulating lesions are present. In 2 out of 4 cases of inoperable carcinoma of the stomach in which dicoumarin was given hematemesis developed. One of them terminated fatally. Two patients with granulating areas being prepared for skin grafting bled from these areas.

Debilitated and cachectic patients had a more prolonged and severe elevation of the prothrombin time than did more vigorous patients.

Twenty hippuric acid liver function tests were done on patients who had received the drug for the most part for a period of a month. Eighteen of these patients showed a normal excretion of hippuric acid. Only 2 showed an excretion less than the expected normal.

SUMMARY

1. Three hundred mg. on two successive days is the suggested basic dose for the prophylactic oral use of dicoumarin.

2. Dicoumarin compound is valuable in the treatment of thrombosis and embolism. Its effect should be maintained for at least four weeks.

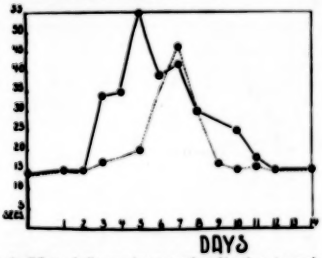

Chart 2.—Effect of dicoumarin on prothrombin time (normal equals 16 seconds). Solid line curve produced with 300 mg. dose given orally daily for first two days; broken line curve produced with 300 mg. the first day, 200 mg. the second day and 200 mg. the fourth day.

3. Dicoumarin compound should be used with caution or not at all in cases in which there are ulcerating lesions.

ABSTRACT OF DISCUSSION

Dr. Alton Ochsner, New Orleans: As clinicians we are certainly indebted to any substance that will lower the incidence of postoperative thrombosis. The greatest use we can derive from dicumarol and heparin is not in the treatment of thrombophlebitis but in its prevention. We have learned to appreciate the value of prevention in postoperative thrombosis but, once thrombosis has occurred, we feel that the anticoagulants have little place. As a matter of fact, I fear that if we pay too much attention to the use of anticoagulants for patients with intravascular clotting we are going to allow those patients to develop emboli. After the thrombus has once occurred, relatively little can be accomplished by giving anticoagulants. The only thing one can hope to do is to prevent further propagation of the clot. In such an instance it is necessary if the patient has a phlebothrombosis, which we like to differentiate from a thrombophlebitis, the former being a condition in which there is a coagulation not associated with an inflammation of the vein, as has been emphasized by Dr. Allen of the Massachusetts General Hospital and his associates, to determine by phlebography the location of the thrombus and to tie off that vein above the site of the thrombus or at least do a phlebectomy. If that is not done, these patients are likely to develop emboli. I have seen 1 patient who had five nonfatal emboli in the course of four weeks, during which time he was getting heparin. The question arises as to whether we are justified in giving dicumarol and heparin to all patients. Obviously we cannot do it with heparin, because it is too expensive. I doubt if it is necessary to give dicumarol to all patients. If a patient gives a history of a previous thrombosis or thrombosis in members of his family, it is desirable to give dicumarol or heparin prophylactically. After the thrombosis has occurred, other measures should be instituted, largely mechanical means, to prevent the loosening of the clot, and if we place too much dependence on the anticoagulants, such as dicumarol and heparin, we are going to lose some patients from the mechanical breaking off of the emboli.

APPENDICITIS IN CLEVELAND

RALPH M. WATKINS, M.D.
Chairman, Survey Committee
CLEVELAND

The study of acute appendicitis, unperforated and perforated, has been conducted by a group of us[1] since the autumn of 1939 by means of a survey of cases in metropolitan Cleveland from Jan. 1, 1930 to Jan. 1, 1942. In those twelve years there occurred 19,401 instances of the affliction in this area, which corresponds to all Cuyahoga County, in which Cleveland is located.

The case records are drawn from the sixteen largest hospitals in the county, and these represent the great majority of all hospital beds in the community.

Diagnosis of the condition in each case is based on the pathologist's report. We did not attempt to analyze any records in which chronic appendicitis or anything similar appeared because of disagreements of criteria. Therefore in this report the cases are grouped under one of three headings: (1) acute simple appendicitis, unperforated, (2) perforative appendicitis with peritonitis and (3) perforative appendicitis with abscess.

A great deal of work has been done for several years in Cleveland as in the rest of the country in educating the layman regarding the dangers of appendicitis. Also much effort has been expended in improving surgical methods and preoperative and postoperative care. We have seen a decline in mortality from the aforementioned classifications of appendicitis from 6.8 per cent in 1930 to 2.8 per cent in 1941. We believe that the aforecited educational efforts are responsible for this gratifying result.

AGE INCIDENCE AND MORTALITY

As is usual, we found few patients among infants and the aged, but high mortalities in these groups. One and five-tenths per cent of the patients were less than 5 years of age but with a death rate of 17 per cent. One and nine-tenths were over 70, with a mortality rate of 34.8 per cent. However, 15.4 per cent were between the ages of 20 and 25, with a death rate of of 1.8 per cent. The complete picture is as follows:

From 0 to 9 years of age, 8.6 per cent of all patients, 8.1 per cent died.

Sponsored by the Cleveland Academy of Medicine and the Cleveland Foundation.

Because of lack of space, this article is abbreviated in The Journal by omission of the tables. The complete article appears in the author's reprints.

The survey has profited greatly by the gratuitous labors of Mr. Howard Whipple Green of the Cleveland Health Council, who has done an enormous bulk of work in analyzing our statistics, and those of Dr. Bruno Gebhard, director of the Cleveland Health Museum, who has designed our exhibit for the scientific sections of the 1941 and 1942 annual sessions of the American Medical Association.

1. The following physicians have been members of the Survey Committee, representing sixteen greater Cleveland hospitals: Drs. D. C. Darrah, R. M. Hosler, H. B. Pevaroff, J. D. Brett, J. H. Lazzari, C. W. Rotter, S. J. Restifo, H. R. Hathaway, W. A. Boukalik, John Keller, John Renshaw, A. F. Sydow, B. B. Larsen, J. M. Rosech, John Budd, S. L. Feldman, R. J. McNamer, P. L. Suhay, George Crile Jr. and Fred Kelly. These persons have done the extracting of case records and have served without compensation.

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From 10 to 29 years of age, 57.4 per cent of all patients, 2.1 per cent died.

Thirty years and over, 34.0 per cent of all patients, 8.6 per cent died.

With regard to delay and mortality our findings were the usual ones (table 2).

INCIDENCE OF THE DISEASE

The disease is on the increase in this section. In 1930 1 person in 832 suffered from it. There has been a gradual increase, figured on population estimates year by year, until, in 1941, 1 in 653 was a victim. The percental yearly rates from 1930 to 1942 have been 0.12, 0.12, 0.12, 0.12, 0.13, 0.13, 0.13, 0.14, 0.14, 0.14, 0.13, 0.15.

LESSENED DELAY IN OPERATION

One of the important reasons for the great decline in mortality is the result of education of the public. The laymen delay their operations so much less that we are meeting fewer cases of peritonitis and abscess and more cases of simple acute appendicitis. This is explained in table 3.

CHANGES IN TYPES OF ANESTHETICS

In 1930 93.5 per cent of the patients received some type of general anesthetic; in 1941 only about 68 per cent were given this. In 1930 only 5 per cent were given spinal anesthesia; in 1941 31 per cent received it. Through the twelve years fewer than 1 per cent were given strictly local anesthesia. Our mortality rates were as follows: for general anesthesia 4.5 per cent, for spinal 5.7 per cent, for local 21.0 per cent. The latter was used only in the worse risks. It is interesting to note the trend in methods, but no conclusions are to be drawn as to the effect on our declining mortality.

DECLINING DRAINAGE IN ACUTE AND PERITONITIS TYPES

We are certain that one of the greatest causes for lowered mortality is the change in the practice of drainage.

It is difficult to believe that in 1930 intraperitoneal drainage was done in 29.8 per cent of the acute simple cases. In that year death occurred in 1.4 per cent of simple cases. So much improvement has occurred that in 1941 drainage was done in only 7 per cent and deaths occurred in 0.3 per cent. Drainage is still done in far too many cases and we hope that the figures will decline rapidly.

In peritonitis the surgeons are using less drainage also. In 1930 drainage was done in 94.9 per cent of these cases, and 22.2 per cent of cases of peritonitis were lost. In 1941 drainage was done in 76.1 per cent and the mortality rate was down to 12.2 per cent. Obviously many peritonitis victims will require drainage, but from the figures it is apparent that as time goes on fewer do. This is perhaps the result of less delay in operation with less extensive involvement of the peritoneum. We hope that in the future there will be less delay, fewer cases of severe peritonitis and consequent less mortality.

Obviously, drainage is done in nearly every case of abscess.

Over the twelve year period drainage was done in 2,301 simple cases with a mortality of 2.7 per cent; drainage was not done in 12,138 simple cases with a mortality of 0.55 per cent. Drainage was done in 2,826 cases of peritonitis with a mortality of 19.6 per cent; drainage was not done in 375 cases of peritonitis with a mortality of 10.9 per cent.

CHANGE IN ECONOMIC STATUS

We have observed definitely that charity patients delay operation an average of twelve hours longer than private patients. Our twelve year death rate of charity patients is 6.5 per cent and for private ones 4.3 per cent, because of this delay. However, there are now fewer charity and more of the private group. This accounts in good part for our decline in mortality. In 1930, 77 per cent were private patients and in 1941, 85 per cent. During the depths of the depression, private patients were down to 71.3 per cent in 1933. There is a corresponding decrease in charity patients from as many as 28.7 per cent in 1933 to 15 per cent in 1941.

THE USE OF THE MC BURNEY TYPE INCISION

Our group is of the opinion that the increased use of the McBurney incision has helped to lower our mortality, because the mortality with its use is much lower than that with other types of incision. This has been true through the twelve years. In 1941, as an example, the death rate with the McBurney type was only half that of other types.

The increase in its use is represented by these figures: In 1930 in 50.3 per cent of the patients the surgeons used this incision. There has been a steady increase, until in 1941 it was employed in 67 per cent of the cases.

ABSCESS: APPENDIX REMOVED AND NOT REMOVED

Over the twelve years in 1,547 cases the appendix was removed at first operation with 12.7 per cent deaths. In 131 cases only drainage was done and the appendix was left in to be removed later. The mortality rate was 11.4 for the primary operation.

THE USE OF SULFONAMIDE DRUGS

We are inclined merely to report our experience with the sulfonamide drugs without drawing any conclusions because our series is made up of too few cases. The sulfonamides have been highly recommended a number of times by others and are without doubt of great value. The drugs were used during the years 1940 and 1941 in all the case types, but in simple acute appendicitis and cases of abscess they were used in too few instances to be worth reporting. The great interest in the use of them is in peritonitis. In 1940 it was not the custom in Cleveland, at least, to use them in peritonitis in any but a general way, that is, by mouth or hypodermically, and even by these means in only about a third of the cases. In 1941 they were used diversely (table 4). These figures are hardly a recommendation for their use, but we wish to state clearly that we were making no special study of the sulfonamides and the report of their use is only incidental to the complete report. Further, there are too few patients involved for it to be profitable for us to make a study of the extent and severity of their infections.

We hope later to have the necessary financial assistance to enable us to publish in complete detail the complex master charts and maze of figures which are the groundwork of the report. When such time arrives they will be available to those students of the disease who may be interested.

SUMMARY

This report consists of the facts gleaned from a study of 19,401 cases of acute unperforated (simple) and perforated (peritonitis and abscess) appendicitis which occurred in greater Cleveland for the years 1930-1941

inclusive. They are based on the pathologic diagnosis and collected from sixteen hospitals and represent nearly all the cases of the disease in that time in this area.

CONCLUSION

Certain facts can be learned from the report. Some are well known. Others are important because they represent reasons why our mortality rate has decreased from 6.8 per cent to 2.8 per cent in twelve years for the types included in the study:

1. Appendicitis is uncommon but highly fatal in the very young and the very old.

2. The longer operation is delayed the higher the mortality.

3. The disease is on the increase in Cleveland.

4. There is a great increase in the use of spinal anesthesia.

5. The removal or nonremoval of the organ at primary operation for abscess is not of great importance as far as our mortality rate shows.

6. Sulfonamides have been used in too few cases to reveal conclusive results in this series. Other workers have proved them to be of great value.

As definite reasons for the great decline in mortality in this series we add the following facts:

7. There is less delay in operation. This is the result of popular and professional education.

8. A gratifying decrease in drainage, especially in acute cases with perforation, is taking place. This trend should continue.

9. More private and fewer charity patients means that part of our good fortune is due to improved economic conditions.

10. The use of the McBurney type incision results in a lower mortality and we are glad to see that its use is on the increase.

10515 Carnegie Avenue.

Clinical Notes, Suggestions and New Instruments

RENAL ISCHEMIA PRODUCED BY ANEURYSM OF ABDOMINAL AORTA

Byron J. Hoffman, M.D., Emory University, Ga.

The experimental investigations of Goldblatt and his associates[1] on dogs in producing renal ischemia and an accompanying hypertensive vascular disease, either benign or malignant, have facilitated a better correlation of pathologic conditions observed in man in which renal ischemia has been produced by involvement of or alterations in the renal artery. The initial studies on experimental hypertension by Goldblatt and his co-workers demonstrated that constriction of the main renal artery of one kidney was followed by an elevation in blood pressure, which usually, but not always, returned to normal within four to eight weeks unless the artery to the other kidney was constricted or the other kidney removed.

However, a few cases of hypertension in man have been observed and reported in which a constricting lesion of one renal artery has apparently been responsible for the coexisting hypertensive vascular disease. Hypertension has been reported in unilateral atherosclerotic narrowing[2] and embolism[3] of the main renal artery, in an aneurysm[4] of the main renal artery, in a dissecting aneurysm of the abdominal aorta with partial occlusion of the renal artery, in a tumor of one kidney[5] with compression of the renal artery and in unilateral pyelonephritis[6] in which the hypertension was partially or completely relieved by removal of the diseased kidney.

The following case is reported because the disease process, which was a saccular aneurysm of the abdominal aorta, produced in man a condition similar to the procedure applied experimentally to animals by Goldblatt and found to be one of the factors responsible for hypertensive vascular disease. The report of a similar case cannot be found.

REPORT OF A CASE

History.—A Negro aged 28 first noticed shortness of breath on exertion during the first part of 1938. This gradually increased in severity and was accompanied by exacerbations of coughing and palpitation. By summer, pedal edema was noted. During the next few months his abdomen gradually increased in size and added to his respiratory difficulty. Because of this dyspnea he could not sleep unless he was propped up in bed or sitting a chair. He was admitted to the Grady Hospital, Emory University division, in December.

His past history was not remarkable. He had been in good health until the onset of dyspnea. A review of the systems was negative except as stated in the present illness.

Physical Examination.—The patient was dyspneic even when propped up to the sitting position. The blood pressure was 190 systolic and 117 diastolic in both arms, pulse rate 100, respiratory rate 28 and temperature 98 F. The pupils were round and equal and reacted to light and in accommodation. The retinal arteries were irregularly constricted and had an increase in light reflex and an arteriovenous ratio of 2 to 3. There were no hemorrhages, exudates or edema of the fundi. The teeth were decayed, the gums dirty and the tonsils slightly enlarged and hyperemic. The neck veins were decidedly distended. Moist rales were present throughout the lungs but were more numerous in the base of each lung. The apex beat was diffuse, being in the fifth and sixth intercostal spaces 10 cm. to the left of the midsternal line. The tones were poor and a soft systolic murmur was present in the mitral area. The abdomen was greatly distended and dull to percussion and gave a positive fluid wave. The lower extremities had 2 plus pitting edema.

Laboratory Results.—The red blood cell count was 4,710,000 per cubic millimeter with 13 Gm. of hemoglobin per hundred cubic centimeters. The white blood cell count was 10,650 with 82 per cent neutrophils and 18 per cent lymphocytes. The sedimentation rate was 25 mm. by the Westergren method. The urine contained a trace of albumin and an occasional pus cell. The blood nonprotein nitrogen was 40 mg. per hundred cubic centimeters, creatinine 2.5 mg. and sugar 76 mg. The serum albumin was 2.9 Gm. and the globulin 2.9 Gm. with a total serum protein of 5.8 Gm. The blood Kahn and Wassermann reactions were positive.

A diagnosis of syphilis with hypertensive heart disease and congestive failure was made. Three thousand cc. of clear slightly yellow fluid was removed from the abdomen by paracentesis. The patient was placed on routine treatment for congestive heart failure, was digitalized and was given a high protein diet and antisyphilitic treatment in the form of weekly

From the Department of Pathology, Emory University School of Medicine.

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injections of bismuth and potassium iodide by mouth. He was dismissed from the hospital greatly improved and advised to continue his newly acquired routine.

Course.—The improvement lasted for several months. During April his symptoms of congestive heart failure returned and fluid began to accumulate within his abdomen. He was readmitted to the hospital on March 15, 1939 and 4,000 cc. of clear fluid was removed by paracentesis. His blood pressure was 170 systolic and 128 diastolic. He was allowed to go home on March 20 but returned on April 6. Another paracentesis yielded 6,000 cc. of fluid.

The symptoms and evidence of congestive heart failure became progressively worse and he was rehospitalized on April 17. The blood pressure at this time was 190 systolic and 110 diastolic, temperature 97 F., pulse rate 95 and respiratory rate 24. A severe generalized anasarca was present. Examination of the fundi revealed slight edema of the retina, with grade 2 to 3 generalized arterial constriction and an arteriovenous ratio of 2 to 3. The lungs contained numerous moist rales, the heart tones were poor without murmurs and the left border of cardiac dulness extended 12 cm. to the left of the midsternal line. There was a 4 plus ascites and severe edema of the lower extremities.

The erythrocyte count was 4,100,000 per cubic millimeter with 10 Gm. of hemoglobin, the leukocyte count being 9,350 per cubic millimeter with 94 per cent neutrophils and 6 per cent lymphocytes. The urine contained 3 plus albumin, numerous red cells, a few pus cells and numerous hyaline and granular casts. The blood nonprotein nitrogen was 42 mg. per hundred cubic centimeters. Paracentesis yielded 6,000 cc. of clear fluid. Reaccumulation of this fluid was rapid and the condition of the patient rapidly became worse, with death occurring on April 24, 1939.

POSTMORTEM EXAMINATION

The abnormal feature on external examination was generalized anasarca. The edema of the face was confined mainly to the periocular subcutaneous tissue. The abdomen was distended with fluid and each flank bulged. There was a 2 plus edema of the sacrum, external genitalia and lower extremities.

The left pleural cavity contained about 600 cc. and the right 900 cc. of clear, slightly yellow fluid having a specific gravity of 1.009. The left lung weighed 520 Gm. and the right 750 Gm. Each on cut section was wet and contained small localized areas of bronchopneumonia in the posterior inferior portions.

The pericardial cavity contained 80 cc. of clear yellow fluid. The left ventricle of the heart was enlarged to the left. The emptied heart weighed 475 Gm. The left ventricular cavity was dilated and the myocardium soft and atonic to palpation. The left ventricular wall averaged 1.9 cm. in thickness and the right 0.4 cm. The valves were normal. The ascending portion of the aorta and the area around the coronary ostiums showed a longitudinal tree bark wrinkling characteristic of syphilitic aortitis. The coronary ostiums appeared to be slightly but distinctly narrowed by the aortitis.

The abdominal cavity contained approximately 5,000 cc. of clear yellow fluid with a specific gravity of 1.012. The inferior edge of the liver was rounded and the hepatic parenchyma had a nutmeg appearance and bulged beneath the cut capsule. The gallbladder wall was moderately edematous. The spleen weighed 160 Gm. and contained numerous old fibrous adhesions over the lateral surface that were attached to the parietal peritoneum. The walls of the gastrointestinal tract were slightly edematous.

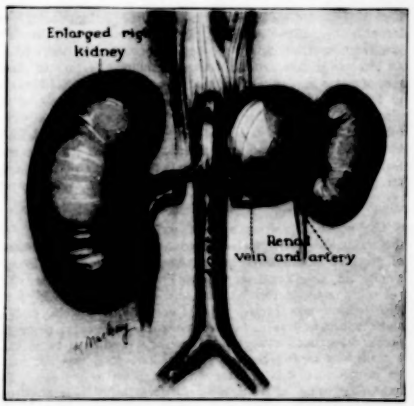
Bulging from the retroperitoneal region just to the left of the midline and below the level of the celiac artery was a mass measuring 6 cm. in diameter. On further exploration this mass was found to be a saccular aneurysm of the posterolateral portion of the abdominal aorta. It was so located as to have become wedged between the abdominal aorta and the left kidney, thereby pushing the left renal artery and vein anteriorly and inferiorly. This is shown in the illustration. In this way the renal vessels were stretched and compressed sufficiently to diminish the lumen of the renal artery considerably. There was no erosion of the renal vessels or of the wall of the aneurysm. About one half of the aneurysm was filled with old organized blood clot.

The left kidney weighed 80 Gm. and on cut section was very red. The capsule stripped with difficulty, leaving a fine granular surface. The cortex averaged 4 to 5 mm. in thickness and the parenchyma 1.5 cm. In contrast, the right kidney weighed 180 Gm. and the capsule stripped with ease, leaving a smooth and glistening surface. The entire parenchyma on cut surface was pale, the cortex averaged 0.9 cm. in thickness and the entire parenchyma 3 cm. in thickness. The calices, pelves and ureters of the two kidneys were normal. The urinary bladder was normal and there was no obstruction to or in the urethra.

Microscopic Examination.—Sections of the lung revealed a diffuse dilatation and engorgement of the alveolar capillaries, scattered areas of intra-alveolar edema, numerous pigment laden phagocytes and a few areas of bronchopneumonia.

Heart sections showed a moderate hypertrophy of the individual muscle fibers, a few small areas of interstitial fibrosis and a moderate degree of diffuse round cell infiltration beneath the epicardium.

An extensive perivascular round cell infiltration was present throughout the sections of the ascending aorta. The media had very little scarring until the region of the coronary ostiums



Position and relative size of the aneurysm and the kidneys.

was reached, but at this site there was a high degree of fibrosis and perivascular infiltration. The sections through the abdominal aneurysm showed a definite intimal thickening, an extensive fibrous tissue replacement of the media and a decided perivascular round cell infiltration throughout the entire wall. The walls of the vasa vasorum were very prominent because of their thickness, with almost complete obliteration of the lumens.

The liver was normal except for a high degree of passive congestion.

The capsule of the pancreas showed considerable perivascular and perilymphatic infiltration. The endothelium of the smaller arteries and arterioles in this area appeared greatly swollen. Many of the arterioles in this section had a moderate degree of subendothelial hyaline thickening.

The spleen had a slight degree of sinusoidal congestion and a moderate intimal thickening of the central arterioles.

The two kidneys differed greatly in microscopic structure. The left had a capsule distinctly thickened with fibrous tissue and several small but prominent arteries in the outer portion. Dilated and engorged capillaries were prominent in the deeper portions and some old blood pigment was scattered throughout the fibrous capsule. The cortex was striking because of the diffuse and severe atrophy of the convoluted tubules. In places many of the atrophic epithelial cells of the convoluted tubules appeared to have undergone a moderate degree of

fatty degeneration. The glomeruli appeared numerous because of the extensive tubular atrophy. Many were completely replaced with hyaline material or had varying degrees of fibrous thickening of Bowman's capsule. All glomerular tufts were diffusely hyperemic and possessed a cellular appearance because of slight proliferation of the capillary endothelium and epithelium. There was also a slight to moderate increase in the basement membrane hyalin. Throughout the cortex and medulla there was a diffuse and severe capillary dilatation and engorgement with erythrocytes. The smaller arteries and arterioles were readily identified because of the thickened media. The interlobular arteries were normal, and there was no subendothelial increase of hyalin in the intima of the terminal arterioles. Albumin filled many of the tubules. A few aggregations of round cells were scattered throughout the cortex. Some of this infiltration was distinctly perivascular.

The right kidney differed greatly from the left. The capsule was thin. The outstanding feature of the cortex was the diffuse and severe dilatation of the convoluted tubules. A few scattered wedge-shaped areas of scarring were present at the periphery of the cortex. The glomeruli were replaced with fibrous tissue and hyaline material and the surrounding tubules were atrophic. An occasional arteriole would show a greatly thickened muscle wall and narrowed lumen. All glomeruli were large. The tufts were large and cellular and had a slight proliferation of the capillary endothelium and epithelium without an increase of intracapillary or intercapillary hyalin. In places the capsular epithelium had undergone sufficient proliferation to form a small crescent. There was no engorgement of the glomerular or interstitial capillaries. A few of the collecting tubules contained red cells, leukocytes or protein material. The large interlobular and small arteries and arterioles were normal except for the arterioles mentioned in the wedge shaped atrophic and scarred areas in the outer portion of the cortex.

COMMENT

The unusual location and the progressive enlargement of the abdominal aneurysm so as to cause an increasing amount of pressure on the left renal vessels offer a condition in man similar to Goldblatt's experimental work on animals. The clinical course of this patient was rapid. Even though the hypertension was severe with a very high diastolic reading and the patient was in his late twenties, there were never the proper eyeground changes and urinary conditions to indicate a malignant nephrosclerosis. Arteriolonecrosis was not found on microscopic study of the sections taken at autopsy. The immediate cause of death was myocardial failure rather than renal insufficiency. The compensatory efforts of the right kidney were apparently physiologically adequate. The slight retention of nonprotein nitrogen material is consistent with a definite passive congestion rather than a primary renal failure.

The syphilitic aortitis with the slight narrowing of the coronary ostiums may have prohibited a greater degree and longer period of compensatory myocardial hypertrophy.

The outstanding feature of the ischemic kidney was the uniform and diffuse atrophy of the nephron unit along with the severe dilatation and engorgement of the glomerular and interstitial capillaries with red cells. The latter accounted for the red appearance noted grossly and can probably be attributed to the venous obstruction caused by compression of the renal vein rather than an inflammatory process. The unusual number of small arteries and the dilated capillaries in the thickened capsule suggest an attempt to establish collateral circulation.

In the right kidney the endothelial and epithelial proliferation of the glomerular tufts and the crescent formation were unaccompanied by other features of glomerulonephritis and were therefore attributed to the proliferation accompanying the compensatory efforts of the right kidney.

SUMMARY

A Negro aged 28 had a saccular aneurysm of the abdominal aorta, syphilitic in origin, which compressed and narrowed the lumens of the left renal vessels. This was accompanied by hypertensive vascular disease and reproduced in man the ingenious experimental work done on dogs by Goldblatt.

Special Article

HANDBOOK OF NUTRITION: X

THE FAT SOLUBLE VITAMINS

HUGH R. BUTT, M.D.
ROCHESTER, MINN.

These special articles on foods and nutrition have been prepared under the auspices of the Council on Foods and Nutrition. The opinions expressed are those of the authors and do not necessarily reflect the opinion of the Council. These articles will be published later as a Handbook of Nutrition.—Ed.

An attempt has been made in the present review to outline a few known facts about each fat soluble vitamin and to mention the most recent advances of general interest that have occurred since publication of the symposium on vitamins sponsored by the American Medical Association in 1939. No attempt has been made to delve into many of the details in this field; rather, data have been presented which it is hoped will be of value in orienting conceptions in a rapidly changing subject.

VITAMIN A

CHEMISTRY AND PHYSIOLOGY

The chemistry and physiology of vitamin A and substances having vitamin A activity have been considered in some detail in previous reviews in THE JOURNAL.[1]

Evidence reveals that there exists, in addition to vitamin A, another compound which has been designated as vitamin A_2. In chemical structure vitamin A_1 is related closely to vitamin A_2; biologically the activity is the same. It appears that vitamin A predominates in the tissues of salt water fish and that vitamin A_2 predominates in the tissues of fresh water fish. The absence of vitamin A_2 in the liver of mammals and other land animals probably can be explained by the absence of vitamin A_2 in their food.[2]

Vitamin A is a fat soluble compound. Apparently, its absorption is facilitated greatly by the simultaneous absorption of a certain amount of fat. Most investigators agree that the presence of bile is not necessary for proper absorption of vitamin A; however, it still is good therapeutic practice to administer bile salts with concentrates of vitamin A in the treatment of patients who have obstruction of the biliary tract. Esters of vitamin A apparently behave in the intestinal tract in a manner similar to the esters of other fatty acids. Apparently they are hydrolyzed by the enzymes present, and during the height of absorption the vitamin exists in the intestinal wall chiefly as an alcohol.[3]

The precursors of vitamin A are all the carotenoid pigments commonly called carotene. Since most of vitamin A comes in the form of carotene, some knowledge of its metabolism is important.

Carotene is absorbed less readily than vitamin A and is subject to several more hazards than vitamin A.

From the Division of Medicine, the Mayo Clinic.

1. Palmer, L. S.: The Chemistry of Vitamin A and Substances Having a Vitamin A Effect, in The Vitamins, Chicago, American Medical Association, 1939, pp. 15-25. Bessey, O. A., and Wolbach, S. B.: Vitamin A: Physiology and Pathology, in The Vitamins, pp. 27-54.

2. Gillam, A. E.: The Vitamin A_1 and A_2 Contents of Mammalian and Other Animal Livers, Biochem. J. **32**: 1496-1500 (Sept.) 1938. Lovern, J. A., and Morton, R. A.: The Distribution of Vitamins A and A_2: III, ibid. **33**: 330-337, 1939. Gray, E. L., and Cawley, J. D.: The Influence of Structure on the Elimination Maximum: The Structure of Vitamin A_2, J. Biol. Chem. **134**: 397-401 (June) 1940.

3. Gray, E. LeB.; Morgareidge, Kenneth, and Cawley, J. D.: Intestinal Absorption of Vitamin A in the Normal Rat, J. Nutrition **20**: 67-74 (July) 1940.

Carotene apparently requires for its absorption the presence of bile in the intestinal tract. In those conditions in which bile is excluded completely or partially from the intestinal tract or whenever there is a deficiency of bile salts, bile must be given as a supplement in order to assure proper absorption. It also has been demonstrated[4] that liquid petrolatum can seriously inhibit absorption of carotene. For this reason, liquid petrolatum should not be given immediately after meals.

Storage.—After absorption, the greater portion of carotene is held in the liver, where it gradually disappears in the Kupffer cells as the concentration of vitamin A in the liver increases. In the case of human beings the content of vitamin A, as in all animals, is much lower in the liver at birth, irrespective of the diet of the mother, than in the liver of a normal adult. The liver probably stores about 95 per cent of the reserve of vitamin A in the body and the amount stored is, as a rule, less during childhood and gradually increases with age.[5] The exact mechanism by which vitamin A is called forth from its reserve store is not known, but from several sources it appears that the distribution of vitamin A in the circulating blood and tissues is controlled in part by the nervous system.[6]

Excretion.—Neither carotene nor vitamin A is excreted by the kidneys unless an excessive dose of either of these substances has been administered. Carotene is readily excreted in the feces but vitamin A is excreted much less readily. Apparently, unutilized excesses of carotene and vitamin A find other channels of excretion or are destroyed in the intestine or elsewhere.

Human milk contains both carotene and vitamin A. The colostrum of the human breast has from two to three times the biologic activity of vitamin A of early milk, and early human milk has from five to ten times the biologic vitamin A activity of cow's milk. Apparently the biologic activity of vitamin A of early human milk is not increased by supplementary administration of cod liver oil to the mother.

It formerly was believed that vitamin A produced a profound effect on the nervous system. However, Wolbach and Bessey[9] have now shown that in vitamin A deficiency in rats, skeletal growth is retarded earlier than that of the soft tissues in general, including that of the central nervous system, and that at least in the white rat the nervous manifestations are due to pressure effects caused by relative overgrowth of the central nervous system.

4. Curtis, A. C., and Klinc, E. M.: Influence of Liquid Petrolatum on Blood Content of Carotene in Human Beings, Arch. Int. Med. **63**: 54-63 (Jan.) 1939. Andersen, O.: Effect of Administration of Liquid Paraffin on the Absorption of Vitamin A in Human Subjects, Hospitalstid. (supp.) **81**: 29-41, 1938; abstr., Nutrition Abstr. & Rev. **8**: 750 (Jan.) 1939.

5. With, T. K.: Undersøgelser over Carotinets Omdannelse til A-Vitamin i Rottens Lever i særdeleh med Henblik paa Processens Hastighed, Nord. med. tidskr. **3**: 2901-2903 (Sept.) 1939. Moore, Thomas: Vitamin A and Carotene: XIII. The Vitamin A Reserve of the Adult Human Being in Health and Disease, Biochem. J. **31**: 155-164, 1937. Ralli, Elaine P.; Papper, Emanuel; Paley, Karl, and Bauman, Eli: Vitamin A and Carotene Content of Human Liver in Normal and in Diseased Subjects: An Analysis of One Hundred and Sixteen Human Livers, Arch. Int. Med. **68**: 102-111 (July) 1941. Cox, A. J., Jr.: Site of Vitamin A Storage in the Liver, Proc. Soc. Exper. Biol. & Med. **47**: 333-335 (June) 1941. Horton, Priscilla B.; Murrill, W. A., and Curtis, A. C.: Vitamin A and Carotene: I. The Determination of Vitamin A in the Blood and Liver as an Index of Vitamin A Nutrition of the Rat, J. Clin. Investigation **20**: 387-393 (July) 1941.

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9. Wolbach, S. B., and Bessey, O. A.: Vitamin A Deficiency and the Central Nervous System, abstr., Am. J. Path. **17**: 586 (July) 1941.

SOURCES, HUMAN REQUIREMENTS AND TOXICITY

Vitamin A is rather widespread in nature in the form of its precursors, the yellow and red carotenoid pigments (provitamins). These pigments are found in the plant world, being distributed from bacteria to garden fruits and vegetables. Pigments, of course, are found chiefly in association with chlorophyll and in the green leaves of plants; this is not invariably true, however, since carrots and sweet potatoes, which are yellow, also are rich in these substances. A few of the more important and rich sources of vitamin A and carotene are green leaf vegetables, green snap beans, spinach, carrots, peas, asparagus, yellow vegetables, eggs, whole milk and whole milk products and apricots.

Vitamin A is fairly stable to heat but is destroyed by oxidation. Foods that are heated for long periods may reveal a rather large loss of potency in vitamin A. Since activity of the vitamin is not affected by boiling, foods cooked in this manner retain their potency. Canned foods and foods stored in the frozen state maintain their maximal value of vitamin A; dried and dehydrated foods, however, show considerable loss.

Human Requirements.—Vitamin A is essential for normal metabolism. Although the exact minimal requirement of vitamin A for man is still unknown, considerable work has been carried out in an effort to settle this point.[10] Since the recommended daily allowances for definite nutrients as defined by the Food and Nutrition Board of the National Research Council and later adopted by the Council on Foods and Nutrition of the American Medical Association represent the thoughts of the leaders in these particular fields, it would seem well that these should be accepted without considering other work in this field in any detail.

For the average man and woman of 70 Kg. and 56 Kg. respectively, the daily allowance is 5,000 international units. In the latter half of pregnancy, 6,000 international units is required, and during lactation 8,000 international units. For children aged less than a year, 1,500 units is required; for those aged 1 to 3 years, 2,000; for those from 4 to 6 years, 2,500; for those from 7 to 9 years, 3,500, and for those from 10 to 12 years, 4,500. For children more than 12 but not more than 15 years of age, 5,000 units is required, and for those from 16 to 20 years of age, 6,000 units. Allowances in all these instances may be less if provided by vitamin A and greater if provided chiefly by the provitamin carotene.

Toxicity.—It is extremely difficult to evaluate the few reports concerning the injurious effects on man following ingestion of cod liver oil. Owing to the general favorable clinical experience obtained in the use of cod liver oil and other preparations containing vita-

10. Booher, Lela E.; Callison, Elizabeth C., and Hewston, Elizabeth M.: An Experimental Determination of the Minimum Vitamin A Requirements of Normal Adults, J. Nutrition **17**: 317-331 (April) 1939. May, C. D.; Blackfan, K. D.; McCreary, J. F., and Allen, F. H., Jr.: Clinical Studies of Vitamin A in Infants and in Children, Am. J. Dis. Child. **59**: 1167-1184 (June) 1940. Lewis, J. M., and Haig, C.: Vitamin A Requirements in Infancy as Determined by Dark Adaptation, J. Pediat. **15**: 812-823 (Dec.) 1939; correction, ibid. **16**: 274 (Feb.) 1940. Booher, Lela E., and Callison, Elizabeth C.: The Minimum Vitamin A Requirements of Normal Adults, the Utilization of Carotene as Affected by Certain Dietary Factors and Variations in Light Exposure, J. Nutrition **18**: 459-471 (Nov.) 1939. Sandels, Cate, Wilkinson and Graves.[11]

min A, extreme care must be taken to be certain that cod liver oil is harmful before its administration is discontinued. Administration of from 50,000 to 300,000 or more U. S. P. units of vitamin A daily for as long as two to six months or more has not been followed by any harmful effects.[11]

EFFECT OF DEFICIENCY OF VITAMIN A

In Relation to Infection.—Few investigators doubt that severe deficiency of vitamin A, or any vitamin, will lower resistance to infection, and almost all will agree that administration of vitamin A during the course of any infection will have little beneficial effect on the outcome unless such a deficiency is present. Some workers believe that the frequency and high mortality rate in pneumonia of infants who are deficient in vitamin A result from a disturbance of function of the mucosa of all parts of the lungs. Others believe that administration of vitamin A in large amounts is beneficial in preventing common infections of the respiratory tract. This subject, however, is in general extremely controversial. Enough evidence indicates that there are many other factors of equal or greater influence in infection than vitamin A and that there is no justification for calling vitamin A the "anti-infection vitamin."

Ocular Changes.—That night blindness is directly related to poor nutrition has been recognized for some time. Experimentally it is now established that vitamin A is the precursor of visual purple as well as the product of its decomposition. Apparently vitamin A unites in the retina with a protein to form visual purple. This, of course, takes place continuously and depends on a sufficient supply of vitamin A. Exposure of the retina to light leads to a chemical change which is reversible but which is not always efficient, and therefore needed supplies of vitamin A must always be available. Not only does vitamin A play a part in metabolism of visual purple (rhodopsin), but it is also important in the formation of visual violet (iodopsin), which is present in the retinal cones.[12] Not only does deficiency of vitamin A produce night blindness but, experimentally, it has been demonstrated that severe deficiency of vitamin A may result in structural breakdown of the retina itself.[13] Night blindness, as recognized clinically, perhaps is associated most frequently with cirrhosis of the liver,[14] gastrocolic fistula [15] and forms of severe chronic diarrhea.

It has been thought that night blindness was one of the earliest symptoms of deficiency of vitamin A, but Kruse [16] suggested recently that even earlier changes of deficiency may be detected by biomicroscopic examination. In a study of 143 persons in the low income group it was reported that 45 per cent had gross and 54 per cent had microscopic ocular lesions (xerosis conjunctivae) characteristic of avitaminosis A. It also was suggested that xerosis conjunctivae probably precedes night blindness as an early sign of deficiency of vitamin A. Kruse suggested that this condition is prevalent in the population at large, and he also pointed out that a vascular reaction of the eyes of these patients is distinct from that noted as a result of deficiency of riboflavin. Others [17] have reported that follicular conjunctivitis occurring among children apparently is a result of deficiency of vitamin A. These workers pointed out that the administration of from 25,000 to 38,000 U. S. P. units of vitamin A daily did not result in any more rapid healing than if only 15,000 U. S. P. units had been given. Apparently, in treatment of conditions with vitamin A, a time factor operates which limits the rate of healing of a lesion. Apparently excessive intake of vitamin A does not increase this rate proportionately.

Epithelium.—Dryness and scaliness of the skin are perhaps some of the earliest manifestations of involvement of the skin resulting from deficiency of vitamin A. Within the past few years several investigators have reported cases in which cutaneous lesions were present and which were considered the result of deficiency of vitamin A.[18] One type of lesion is characterized by small pustules which appear around the hair follicles or extensor surfaces of the upper and lower extremities, on the shoulder and on the lower part of the abdomen and buttocks. These pustules vary in diameter up to 5 mm., are hard and deeply pigmented and have a surrounding zone of deep pigmentation. An epithelial plug is in the center of the lesion which, when expressed, leaves a crater. Other writers have described a type of lesion which resembles in many ways the pustule of acne, with the exception that pustulation is uncommon. It is believed [19] that keratosis pilaris, ichthyosis follicularis and other synonyms are descriptive terms for the cutaneous manifestations of deficiency of vitamin A. In treatment of such conditions daily doses of 100,000 to 300,000 international units of vitamin A is given for two or three months before beneficial effects are noted. It is pointed out that response of cutaneous lesions to vitamin A is slow, depending as it does on anatomic repair.

Recently [20] evidence has been reported which indicates that vernix caseosa is a manifestation of deficiency of vitamin A of newborn infants and that it represents disturbances in cornification analogous to the dermal changes noted in other manifestations of deficiency of vitamin A. This work has not yet been confirmed.

A majority of investigators have failed to find any relation between the presence of calculi in the urinary tract and a diet deficient in vitamin A, in spite of suggestive experimental evidence in this direction.[21]

Liver.—It has been established that the liver plays a major role in the metabolism of vitamin A, but the exact manner in which this is accomplished is not known. It has been known for many years that keratomalacia and night blindness accompany diseases of the liver, and recently these conditions have been reported [22] in association with obstructive biliary cir-

11. Straumfjord.[20] Lehman and Rapaport.[19]
12. Wald, George, and Steven, David: An Experiment in Human Vitamin A Deficiency, Proc. Nat. Acad. Sc. **25**: 344-349 (July) 1939.
13. Johnson, Myra L.: The Effect of Vitamin A Deficiency on the Retina of the Rat, J. Exper. Zool. **81**: 67-89 (June) 1939.
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15. Butt, H. R.: Unpublished data.
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17. Sandels, Margaret R.; Cate, Helen D.; Wilkinson, Kathleen P., and Graves, L. J.: Follicular Conjunctivitis in School Children as an Expression of Vitamin A Deficiency, Am. J. Dis. Child. **63**: 101-114 (July) 1941.
18. Rao, M. V. R.: Treatment of Phrynoderma by Vitamin A Concentrate, Indian M. Gaz. **73**: 461-462 (Aug.) 1938. Lehman and Rapaport.[19]
19. Lehman, Edward, and Rapaport, H. G.: Cutaneous Manifestations of Vitamin A Deficiency in Children, J. A. M. A. **114**: 386-393 (Feb. 3) 1940.
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rhosis. Others [23] have demonstrated deficiency of vitamin A in cirrhosis of the liver not associated with jaundice. Many others have demonstrated repeatedly that the vitamin A in the liver and blood of patients who have severe hepatic injury nearly always is decreased considerably.[24] It has been suggested that since pathologic conditions of the liver result in incomplete transformation of carotene into vitamin A, fish liver oil should be given in preference to carotene in the treatment of hepatic disease.[25]

It is obvious that deficiency of vitamin A also may result from poor absorption of the vitamins, such as may occur in diarrhea,[26] celiac disease [27] and various diseases of the liver in which the flow of bile is disrupted.[28]

METHODS FOR MEASURING DEFICIENCY OF VITAMIN A

Dark Adaptation.—The fact that night blindness is an early symptom of deficiency of vitamin A led to the development of visual adaptation in dim light as a method for the diagnosis of deficiency of vitamin A. Whether deficiency of vitamin A can be measured by testing adaptation to dark continues to be a most controversial subject. Some contend that this method is satisfactory for measuring deficiency of vitamin A.[29] Others [30] contend that, although some relation exists between readings of the biophotometer and of nutrition of vitamin A, yet the relation is not close enough to warrant use of the test as a means of diagnosis of subclinical deficiency of vitamin A. It has been pointed out that the method is time consuming, and for this reason alone its routine clinical use practically is ruled out. Certainly, minor fluctuations in dark adaptation in terms of deficiency of vitamin A should receive little emphasis unless the physical methods are used to test the reliability of the differences. It is true that a majority of workers believe that the study of dark adaptation can be used as a test for deficiency of vitamin A, but until differences in technic and in interpretation of results have been resolved it is impossible to be certain how far recorded observations represent physiologic facts. In fact, by placing human beings on a diet deficient in vitamin A over long periods, some investigators [31] have been unable to produce clinical night blindness or even changes in dark adaptation. It may be, as stated by Josephs,[32] that all this discrepancy may be the result of lack of knowledge of methods for determining sufficient storage of vitamin A.

No definite correlation between biophotometer readings and the content of vitamin A in the blood has been observed.[33] Although it has been demonstrated that the amount of vitamin A in the blood is dependent on the amount in the diet, yet evidence as to whether determination of vitamin A in the blood is of value in judging the nutritional status is still contradictory. Recently evidence has been presented which suggests that the concentration of vitamin A in the blood plasma is a considerably more sensitive indicator of deficiency of vitamin A than the dark adaptation.[34]

The same contradictory evidence is presented for measuring vitamin A by examination of scrapings from the eye and vagina. From all these studies it would be judged that the methods for measuring deficiency of vitamin A of man still are somewhat unreliable and demand further study. Among some physicists and chemists there still is doubt whether the small quanti-

23. Patek, A. J., Jr., and Haig, Charles: The Occurrence of Abnormal Dark Adaptation and Its Relation to Vitamin A Metabolism in Patients with Cirrhosis of the Liver, J. Clin. Investigation **18**: 609-616 (Sept.) 1939.

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(Footnote 30 in next column)

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ties of vitamin A present in the blood stream of man can be measured with the chemical methods available. There are others who feel that no satisfactory chemical methods can be developed until the storage capacity of the body for vitamin A can be estimated in some degree.

VITAMIN D

Since the time (1922) of McCollum's demonstration that vitamin D is distinct from vitamin A, this vitamin (D) has received perhaps the greatest universal attention of any. Here, in the early history of nutritional investigation, was found a substance which was of value in the prevention and cure of a disease.

CHEMICAL ASPECTS

Some ten forms of vitamin D are known, but only two of them are of practical importance. One is ergosterol, which on exposure to ultraviolet light becomes viosterol (a name adopted by the Council on Pharmacy and Chemistry of the American Medical Association). The other form of vitamin D of practical use is activated 7-dehydrocholesterol. This substance is present in animal fats, and its active form is produced in the skin, feathers or furs of animals exposed to sunlight or other sources of ultraviolet waves.[33] Successful synthesis of compounds related to the antirachitic vitamins has been reported, and it is hoped that a suitable product soon will be available.[34]

PHYSIOLOGIC ASPECTS

The active vitamin D formed in the skin is absorbed by the blood. When the vitamin is ingested it is readily absorbed from the intestinal tract if adequate amounts of bile salts are present. Results of recent investigations indicate that the salts of desoxycholic acid may be particularly concerned with the absorption of the liposoluble vitamins.

The chief storehouse of vitamin D in the human being is the liver, but significant amounts are stored also in the skin, brain, lungs, spleen and bones.[37] Moreover, although the liver is the chief storehouse of the vitamin, normal hepatic function is necessary to promote the antirachitic action of vitamin D.

The body apparently has great powers for the conservation of vitamin D. Studies on the excretion of vitamin D are lacking, but it is known that small doses of vitamin D will exert an influence which endures for several weeks and that large doses of it are carefully preserved for a long time.

Concentration of vitamin D in the blood has been studied inadequately, and in view of methods presently available such studies are impracticable for even a well equipped laboratory to carry out.[38]

The exact role of vitamin D in the metabolism of calcium and phosphorus still is not fully established. The action of vitamin D on calcium and phosphorus metabolism, however, seems to be concerned chiefly with absorption of the elements from the intestinal tract. In carefully conducted studies,[39] it has been reported that one of the first signs of deficiency of vitamin D is the decrease in the amount of calcium in the urine, followed by an increase of calcium in the stool which progresses with the deficiency until a negative calcium balance exists. The changes in the metabolism of phosphorus differ only in the fact that the urinary excretion of phosphorus is increased. These changes can be reversed with very small doses of vitamin D. Results of other studies tend to confirm these observations.[40]

There exists in the body an enzyme, phosphatase, which is related intimately to phosphorus metabolism. Its exact function in the serum is not known, but in active rickets the value for phosphatase in the serum is high. The administration of vitamin D under these circumstances decreases the concentration toward normal but more slowly than it increases the concentration of calcium and phosphorus.

DISTRIBUTION, HUMAN REQUIREMENT AND TOXICITY

Vitamin D is an essential vitamin but is contained in only a few of the foods in the average American diet. Small amounts are present in eggs, herring, sardines, tuna and salmon, either fresh or canned.[41] Contrary to a popular misconception, butter contains only a very small amount of vitamin D.

Since the average diet furnishes so little vitamin D, it must be assumed either that the requirement of vitamin D for man is extremely low or that his needs usually are provided by exposure to sunshine. The requirement of vitamin D during adult life, therefore, remains to be determined. Vitamin D undoubtedly is necessary for older children and adult persons, and when not available from sunshine it should be provided, probably up to the minimal amounts recommended for infants. During pregnancy and lactation and for children under a year of age, 400 to 800 international units of vitamin D is the daily requirement recommended by the Food and Nutrition Board of the National Research Council. In administering antirachitic agents the physician should think in terms of units of vitamin D, since this is the only way in which the doses of the various substances containing vitamin D, which differ greatly in volume, can be reduced to a common denominator.

When doses of vitamin D many times the therapeutic dose are administered to animals, certain pathologic changes are noted. In the human being, however, no serious toxic effects have been reported in cases in which doses of as much as 1,000,000 units have been administered to rachitic children.[42] Some adult persons treated with large doses of vitamin D have complained of nausea, headache, diarrhea, anorexia, urinary frequency and lassitude. If renal insufficiency exists, it might be feared that some degree of toxicity would result from overdosage with vitamin D.[43]

33. Bills, C. E.: The Chemistry of Vitamin D, in The Vitamins, Chicago, American Medical Association, 1939, pp. 443-458.

36. Milas, N. A., and Alderson, W. L., Jr.: Studies in the Synthesis of the Antirachitic Vitamins: I. The Synthesis of 3-[2'Methylenecyclohexylidene-1']-Propene-1, J. Am. Chem. Soc. **61**: 2534-2537 (Sept.) 1939. Aldersley, J. B.; Burkhardt, G. N.; Gillam, A. E., and Hindley, N. C.: The Synthesis of Compounds Related to the Antirachitic Vitamins: Part II, J. Chem. Soc. London, part 1 (Jan.) 1940, pp. 10-16.

37. Vollmer, Hermann: Distribution of Vitamin D in Body After Administration of Massive Doses, Am. J. Dis. Child. **57**: 143-148 (Feb.) 1939. Vollmer, Hermann: Distribution of Vitamin D in the Brain After Repeated Administration of Massive Doses; Histologic Investigation of D-Hypervitaminosis, Arch. Pediat. **58**: 9-20 (Jan.) 1941.

38. Warkany, Josef, and Mahon, Helen E.: Estimation of Vitamin D in Blood Serum: II. Level of Vitamin D in Human Blood Serums, Am. J. Dis. Child. **60**: 606-614 (Sept.) 1940.

39. Liu, S. H.: The Role of Vitamin D in the Calcium Metabolism in Osteomalacia, Chinese M. J. **57**: 101-118 (Feb.) 1940. Liu, S. H.; Chu, H. I.; Su, C. C.; Yu, T. F., and Cheng, T. Y.: Calcium and Phosphorus Metabolism in Osteomalacia: IX. Metabolic Behavior of Infants Fed on Breast Milk from Mothers Showing Various States of Vitamin D Nutrition, J. Clin. Investigation **19**: 327-347 (March) 1940. Chu, H. I.; Liu, S. H.; Yu, T. F.; Hsu, H. C.; Cheng, T. Y., and Chao, H. C.: Calcium and Phosphorus Metabolism and Osteomalacia: X. Further Studies on Vitamin D Action: Early Signs of Depletion and Effect of Minimal Doses, ibid. **19**: 349-363 (March) 1940.

40. Albright, Fuller; Sulkowitch, H. W., and Bloomberg, Esther: A Comparison of the Effects of Vitamin D, Dihydrotachysterol (A. T. 10), and Parathyroid Extract on the Disordered Metabolism of Rickets, J. Clin. Investigation **18**: 163-169 (Jan.) 1939.

41. Lindsay, Jessie, and Mottram, V. H.: Vitamin D in Diet: Palatable Methods of Supply, Brit. M. J. **1**: 14-15 (Jan. 7) 1939.

42. Gunnarson, Sav: Treatment of Rickets with a Single Massive Dose of Vitamin D_2, Acta paediat. **25**: 69-81, 1939.

43. Opper, Lincoln: Effect of Renal Damage on the Toxicity of Hypervitaminosis D in Rats, Arch. Path. **31**: 569-577 (May) 1941.

CLINICAL USE

Little can be added to the comprehensive article by Jeans and Stearns[44] on the clinical usefulness and available sources of vitamin D which appeared in the symposium on vitamins sponsored by the American Medical Association in 1939. This and several other comprehensive reviews[45] deal most adequately with this problem, and there seems little need of much repetition. Other sections to be presented in this review also will deal with the clinical use and value of vitamin D.

The suggestion made by Park,[46] however, in the treatment of rickets will again bear emphasis. For preventive measures the importance of commencing administration of the vitamin early and reaching the full dose "certainly by the end of the second month" of the infant's life cannot be repeated too often. In the active treatment of rickets, milk containing vitamin D does not exhibit sufficient activity to end the disease abruptly, and doses of vitamin D sufficient to furnish 1,000 U. S. P. units daily, or even 10,000 to 20,000 units to premature infants, may be required.

The treatment of active rickets with large, single parenteral doses of vitamin D has received considerable attention during the past two years.[47] Administration of 500,000 to 1,000,000 U. S. P. units of vitamin D to children who had rickets (including premature infants) has been followed by rapid healing without clinical evidence of toxicity.

Many other diseases unrelated to rickets have been reported as benefited by the administration of vitamin D. Pemphigus,[48] chronic ulcers of the extremities[49] and psoriasis[50] are only a few conditions reported as benefited thereby. Most of the results reported have not been confirmed.

VITAMIN E

When it is compared to the other vitamins, vitamin E assumes a rather unsatisfactory position, since it has never been demonstrated that a deficiency of this substance occurs in man. As early as 1922 the necessity of this factor (then called "factor X") was recognized in animals, and in spite of a host of brilliant chemical and physiologic discoveries clinical attempts at application of this knowledge have resulted only in controversy.

CHEMICAL AND PHYSIOLOGIC PROPERTIES

Recent advances in the knowledge of vitamin E have been confined in a large measure to the field of chemistry and experimental animal physiology. Details of these advances may be found in journals or books devoted to this subject.[51] Suffice it herein to say that there are now more than one hundred and thirty compounds which exhibit vitamin E activity. The most active of these compounds are the tocopherols. The tocopherols are readily soluble in lipoid solvents, resist high temperatures and lose their activity in the presence of mild oxidizing agents. It has been postulated that in the living organism vitamin E might act as a respiratory enzyme.

In animals a lack of vitamin E manifests itself chiefly by changes which it causes in the reproductive mechanism and in the muscular and nervous systems. In the female rat conception is followed by "resorptive sterility," and in the male rat degeneration of the germinal epithelium and spermatozoa develops to the point of complete loss of reproductive power. Absence of vitamin E in certain animals (rabbits and guinea pigs) is followed by muscular dystrophy and a characteristic paralysis of the hindquarters. In other animals (chicks) encephalomalacia and exudative diathesis may develop.

The possible relationship of vitamin E to the glands of internal secretion and to the growth of tumors has stimulated a great amount of experimental work, but results are completely controversial.[52]

Several methods exist for the chemical and biologic estimation of vitamin E, but they are of little importance to the clinician.

SOURCES, HUMAN REQUIREMENT AND TOXICITY

Wheat germ oil is the richest source of vitamin E, but this vitamin also is found in considerable amounts in cottonseed oil, lettuce oil, rice germ oil and other seed germ oils. The human requirements of vitamin E are completely unknown.

No toxic reactions have been reported in cases in which small doses were administered, and large doses of wheat germ oil have given rise only to minor symptoms. The danger of the production of neoplasms after the continued ingestion of large doses of tocopherols appears to be nonexistent.

CLINICAL USE

If the physician makes only a cursory appraisal of the current literature he may be led to believe that in vitamin E he has a potent weapon for his attack on habitual abortion, sterility, menstrual disturbances and various myoneurogenic diseases. A critical analysis of these numerous reports, however, tends to stem overenthusiasm.[53]

44. Jeans, P. C., and Stearns, Genevieve: The Human Requirement of Vitamin D, in The Vitamins, Chicago, American Medical Association, 1939, pp. 483-512.

45. Kramer, Benjamin: Vitamin D Therapy, J. Mt. Sinai Hosp. **8:** 188-209 (Sept.-Oct.) 1941. Park.[46]

46. Park, E. A.: The Therapy of Rickets, J. A. M. A. **115:** 370-379 (Aug. 3) 1940.

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48. King, Howard, and Hamilton, C. M.: Pemphigus Controlled by Vitamin D, Arch. Dermat. & Syph. **39:** 515-517 (March) 1939.

49. Brandaleone, Harold: The Effect of the Direct Application of Cod Liver Oil on the Healing of Ulcers of the Feet in Patients with Diabetes Mellitus, Ann. Surg. **108:** 141-152 (July) 1938.

50. Krafka, Joseph: Vitamin D Therapy in Psoriasis, J. M. A. Georgia **30:** 398-400 (Sept.) 1941.

51. Mattill, H. A.: Vitamin E, in The Vitamins, Chicago, American Medical Association, 1939, pp. 575-596. Smith, L. I.: The Chemistry of Vitamin E, Chem. Rev. **27:** 287-329 (Oct.) 1940. Vitamin E, New York, Chemical Publishing Co., Inc., 1940. Evans, H. M.; Emerson, O. H.; Emerson, G. A.; Smith, L. I.; Ungnade, H. E.; Prichard, W. W.; Austin, F. L.; Hoehn, H. H.; Opie, J. W., and Wawzonek, S.: The Chemistry of Vitamin E. XIII. Specificity and Relationship Between Chemical Structure and Vitamin E Activity, J. Organ. Chem. **4:** 376-388 (Sept.) 1939. Ridgway, R. R.; Drummond, J. C., and Wright, Mar-

(Footnote 51 continued in next column)

garet D.: The Biological Activity of the Oxidation Products of α-Tocopherol, Biochem. J. **34:** 1569-1573 (Dec.) 1940. Tishler, Max, and Evans, H. M.: Vitamin E Activities of Some Compounds Related to α-Tocopherol, J. Biol. Chem. **139:** 241-245 (May) 1941. Pappenheimer, A. M.: Certain Nutritional Disorders of Laboratory Animals Due to Vitamin E Deficiency, J. Mt. Sinai Hosp. **7:** 65-76 (July-Aug.) 1940. Pappenheimer, A. M., and Goettsch, Marianne, with the assistance of Karsubova, Claudia: Effect of Nerve Section on Development of Nutritional Muscular Dystrophy in Young Rats, Proc. Soc. Exper. Biol. & Med. **43:** 313-316 (Feb.) 1940. Anderson, H. D.; Elvehjem, C. A., and Gounce, J. E., Jr.: Vitamin E Deficiency in Dogs, ibid. **42:** 750-755 (Dec.) 1939. Friedman, Irving, and Mattill, H. A.: The Oxygen Consumption of Skeletal Muscle from Animals Deprived of Vitamin E, Am. J. Physiol. **131:** 593-600 (Jan.) 1941. Mackenzie, C. G.; Mackenzie, J. B., and McCollum, E. V.: Uncomplicated Vitamin E Deficiency in the Rabbit and Its Relation to the Toxicity of Cod Liver Oil, J. Nutrition **21:** 225-234 (March) 1941. Dam, Henrik; Glavind, Johannes; Inge, Prange, and Ottesen, J.: Some Studies on Vitamin E, Biologiske Meddelelser, 1941, vol. 16. Mackenzie, C. G., and McCollum, E. V.: The Cure of Nutritional Muscular Dystrophy in the Rabbit by Alpha-Tocopherol and Its Effect on Creatine Metabolism, J. Nutrition **19:** 345-362 (April) 1940. Adamstone, F. B.: Brain Degeneration in Young Chicks Reared on an Iron-Treated Vitamin E-Deficient Ration, Arch. Path. **31:** 603-612 (May) 1941.

52. Drummond, J. C.; Noble, R. L., and Wright, M. D.: Studies on the Relationship of Vitamin E (Tocopherols) to the Endocrine System, Endocrinology **1:** 275-286 (Nov.) 1939. Biddulph, C., and Meyer, R. K.: The Influence of Vitamin E-Deficiency on the Endocrine Glands of Rats, Particularly on the Gonadotropic Hormone Content of the Pituitary Gland, Am. J. Physiol. **132:** 259-271 (Feb.) 1941.

53. The Treatment of Habitual Abortion with Vitamin E, Report of the Council on Pharmacy and Chemistry, J. A. M. A. **114:** 2214-2218 (June 1) 1940. Evans, H. M.: The William Henry Welch Lectures: New Light on the Biological Role of Vitamin E, J. Mt. Sinai Hosp. **6:** 233-244 (Jan.-Feb.) 1940.

The Reproductive System.—A number of papers in which the treatment of habitual abortion with vitamin E is considered have appeared, but when one considers the inherent difficulty of making the diagnosis of habitual abortion, plus the absence of knowledge of the outcome in cases in which treatment is completely lacking, then one is impressed with the almost complete futility of attempting to arrive at any justifiable conclusion. The physician, however, must not become iconoclastic but must keep an open mind on this subject and await results of further study.[54]

Vitamin E has been used in the treatment of various other disturbances of the reproductive system, including male and female sterility, menstrual disturbances, toxemias of pregnancy, faulty lactation and vaginal pruritus. The reported results are at variance and cannot be accepted until further evidence has been accumulated.

Myoneurogenic Disturbances.—During the past two years clinicians have concerned themselves with the possible benefit of vitamin E in the treatment of various neuromuscular disturbances. The encouragement aroused by early reports [55] on the treatment of amyotrophic lateral sclerosis with vitamin E was short lived. More extensive studies soon followed and the results were discouraging [56] in treatment of both amyotrophic lateral sclerosis and various forms of dystrophy. Wechsler's reports,[57] however, continue to show favorable results in the treatment of amyotrophic lateral sclerosis. He suggested that the therapeutic doses previously used were too small and implied that 150 to 300 mg. given intramuscularly, and 200 mg. or more given by mouth, might be an adequate daily dose of alpha-tocopherol.

Since investigation in this field is relatively new, physicians must completely reserve their answer to the question "What can we expect of vitamin E in the treatment of human myoneurogenic disturbances?"

VITAMIN K

In the review of vitamins sponsored by the American Medical Association in 1939, vitamin K appeared under the section entitled "Other factors: less well known vitamins." This fact in itself emphasizes how rapid has been the increase in knowledge of this vitamin. In this brief review no attempt will be made to mention the large volume of literature which has accumulated on this subject during the past three years. For details and an extensive bibliography the reader is referred to recent monographs and reviews on the subject.[58]

CHEMISTRY AND PHYSIOLOGY

Chemistry.—In May 1939 McKee and his associates reported the isolation of vitamin K_1 from alfalfa and of vitamin K_2 from putrefied fish meal and presented evidence to indicate a quinoid structure of these vitamins. Independently, several groups of investigators reported the structure of the vitamin K_1 molecule to be 2-methyl-3-phytyl-1,4-naphthoquinone. Vitamin K_2 has not yet been prepared synthetically, nor has its true structure been determined. Both vitamins are fat soluble, and exposure of the pure preparation to sunlight and artificial light results in a loss of the activity of the vitamin. The activity also is destroyed by alkalis and strong acids. Fieser and his associates have investigated nearly every possible modification of the vitamin K_1 molecule, and in every instance the change is attended with a distinct diminution in biologic potency.[59]

Soon after it was demonstrated that vitamin K_1 and K_2 possessed a quinoid structure, other compounds possessing this structure were investigated. It was found that of all the compounds studied 2-methyl-1,4-naphthoquinone (menadione) proved to possess the strongest antihemorrhagic activity. By the chick assay method this compound has been found to be about three times as potent as vitamin K_1, at least on a basis of weight. Menadione is so active that several investigators have suggested that it be adopted as a basic standard assay of vitamin K. Because of the wide usefulness of this compound in clinical medicine, the Council on Pharmacy and Chemistry of the American Medical Association, on the recommendation of the Committee on Nomenclature, authorized menadione as a nonproprietary name for this substance.[60]

Physiology.—Pure vitamin K_1 has not been available long enough to allow complete knowledge of its physiologic action to be collected. It has been suggested that vitamin K acts as a reversible oxidation reduction catalyst. It has been suggested that the reversible character of the vitamin may be used to explain the fact that small quantities are effective clinically. It is known, however, that the vitamin is associated in some way with the integrity of the hepatic parenchyma and with the metabolism of prothrombin.

The presence of adequate amounts of bile salts is required for proper absorption of vitamin K. Recently, it has been emphasized that excessive amounts of liquid petrolatum administered with meals may prevent proper absorption of this vitamin. Clinical experience with this vitamin indicates that it is not absorbed through the colon or upper part of the ileum but that it is absorbed readily through the upper part of the jejunum.

The vitamin apparently is not stored easily in the body, and clinical work indicates that what little is stored in the body is in the liver.

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55. Bicknell, Franklin: Vitamin E in the Treatment of Muscular Dystrophies and Nervous Diseases, Lancet **1**: 10-13 (Jan. 6) 1940. Wechsler, I. S.: Recovery in Amyotrophic Lateral Sclerosis Treated with Tocopherols (Vitamin E): Preliminary Report, J. A. M. A. **114**: 948-950 (March 16) 1940. Stone, Simon: Treatment of Muscular Dystrophies and Allied Conditions: Preliminary Report on Use of Vitamin E (Wheat Germ Oil), ibid. **114**: 2187-2191 (June 1) 1940.

56. Shelden, C. H.; Butt, H. R., and Woltman, H. W.: Vitamin E (Synthetic Alpha-Tocopherol) Therapy in Certain Neurologic Disorders, Proc. Staff Meet., Mayo Clin. **15**: 577-580 (Sept. 11) 1940. Doyle, A. M., and Merritt, H. H.: Vitamin Therapy of Diseases of the Neuromuscular Apparatus, Arch. Neurol. & Psychiat. **45**: 672-679 (April) 1941. Denker, P. G., and Scheinman, Leonard: Treatment of Amyotrophic Lateral Sclerosis with Vitamin E (Alpha-Tocopherol), J. A. M. A. **116**: 1893-1895 (April 26) 1941. Ferrebee, J. W.; Klingman, W. O., and Frantz, A. M.: Vitamin E and Vitamin B_1: Clinical Experience in the Treatment of Muscular Dystrophy and Amyotrophic Lateral Sclerosis, ibid. **116**: 1895-1896 (April 26) 1941. McIlwyde, Angus, and Baker, L. D.: Vitamin Therapy in Progressive Muscular Dystrophy: Vitamin B_1, Other Factors of the B Complex, and Vitamin E, J. Pediat. **18**: 727-731 (June) 1941. Worster-Drought, C., and Shafar, J.: Motor Neurone Degeneration Treated with Vitamin E, Lancet **2**: 209-212 (Aug. 23) 1941. Harris, M. M.: Negative Therapeutic and Metabolic Effects of Synthetic Alpha-Tocopherol (Vitamin E) in Muscular Dystrophy, Am. J. M. Sc. **202**: 258-264 (Aug.) 1941. Fitzgerald, Gerald, and McArdle, Brian: Vitamins E and B_1 in the Treatment of Muscular Dystrophy and Motor Neurone Disease, Brain **64**: 19-42 (March) 1941.

57. Wechsler, I. S.: The Treatment of Amyotrophic Lateral Sclerosis with Vitamin E (Tocopherols), Am. J. M. Sc. **200**: 763-778 (Dec.) 1940. Wechsler, I. S.: Amyotrophic Lateral Sclerosis Treated with Synthetic Vitamin E, Arch. Neurol. & Psychiat. **45**: 873-875 (May) 1941.

58. Butt, H. R., and Snell, A. M.: Vitamin K, Philadelphia, W. B. Saunders Company, 1941. Brinkhous, K. M.: Plasma Prothrombin; Vitamin K, Medicine **19**: 329-416 (Sept.) 1940. Bay, Ricardo: Higado-protrombina-vitamina K: (estudio experimental y clinico), Buenos Aires, Univ., Inst. de Clin. Quir., Bol. **17**: 139-231 (Feb.-March) 1941. Koller, Fritz: Das Vitamins K und seine klinische Bedeutung, Leipzig, Georg Thieme, 1941.

59. Fieser, L. F.: The Chemistry of Vitamin K, Ann. Int. Med. **15**: 648-658 (Oct.) 1941.

60. Menadione, Nonproprietary Term for the Substance 2-Methyl-1, 4-Naphthoquinone, Report of Council on Pharmacy and Chemistry, J. A. M. A. **116**: 1054 (March 15) 1941.

So far as is known, vitamin K is not present in the urine but it can be demonstrated in the feces. Whether it is there because organisms are present in the feces which are known to contain vitamin K or whether the presence of the vitamin in feces is referable to real excretion of vitamin K remains to be established.

So far as is known, vitamin K at present has no relation to immunity, infection, pregnancy, lactation or the nervousness associated with diseases of the gastrointestinal tract or cardiovascular system. It is associated intimately, however, with normal physiologic function of the liver and with proper coagulation of the blood. Its exact role in coagulation of blood is not known. Vitamin K is known to be necessary for proper formation of prothrombin, but in what manner this is accomplished remains to be determined. A deficiency of vitamin K from any cause produces a deficiency of prothrombin in the circulating blood, and in all instances, except those in which severe hepatic damage is present, this deficiency of prothrombin can be corrected by proper administration of vitamin K or synthetic compounds which possess antihemorrhagic activity.[61]

SOURCES, HUMAN REQUIREMENTS AND TOXICITY

Vitamin K is distributed widely in nature, and among its richest sources are green leaves of different kinds. Alfalfa and spinach are rich in the vitamin, and cabbage, cauliflower, carrot tops, soy bean oil and seaweed are all good sources. Less abundant sources are tomatoes, orange peel and hemp seed. Seeds, fruits and roots in general contain considerably less vitamin K than do green leaves of different kinds. Parts of the plant that contain chlorophyll usually have the largest amount of vitamin K. The vitamin also is found in a number of bacteria, and during growth of bacteria the vitamin apparently is synthesized and retained.[58]

The exact minimal requirements of vitamin K for infant, child, mother or normal adult have not yet been determined. It has been suggested that the requirement of vitamin K for newborn infants is extremely low and that possibly 1 microgram of synthetic vitamin K is a sufficient daily amount. It has been pointed out that there is no relationship between the mother's diet and the postpartum level of prothrombin of newborn infants. Apparently a completely adequate diet for the pregnant woman, as it is understood today, is not sufficient to protect the child from the potential dangers of hemorrhage resulting from a deficiency of prothrombin. It is known, however, that pure vitamin K_1 or a synthetic compound exhibiting vitamin K activity, in doses of from 1 to 2 mg., is capable of correcting deficiency of vitamin K in most instances. This dose, however, apparently depends on the degree of hepatic damage present. It is known that diarrhea and inadequate intestinal absorption will increase the need for vitamin K. This general lack of knowledge of requirements for vitamin K undoubtedly will be corrected as soon as methods are developed by which vitamin K can be measured in biologic material.

Toxicity.—To date no serious untoward reaction has been observed among persons who have received reasonable therapeutic doses of either natural concentrates of vitamin K, synthetic vitamin K_1 or any of the synthetic compounds exhibiting antihemorrhagic activity now available commercially. An effect has not been noted on blood pressure, respiration, permeability of capillaries or urinary excretion following administration of any of these compounds. It has been observed, however, that doses of menadione as large as 180 mg. administered orally to human beings result in vomiting and porphyrinuria. These huge doses, however, are so obviously greater than those employed for therapeutic use that at present it appears safe to continue therapeutic administration of these synthetic compounds. Fieser wisely pointed out that some clinical consideration should be given to the possible conflict or otherwise undesirable characteristics which may be associated with conjugates resulting from administration of menadione. He pointed out that the delayed action of the administered material would appear to be subject to considerable uncertainty, and the wide opportunity for transformation of different types would lead one to expect a variability in the response, depending on the manner of administration and the condition of the patient.[62]

METHODS FOR MEASURING DEFICIENCY OF VITAMIN K IN MAN: ASSAY METHODS, UNITAGE AND BIOLOGIC METHODS

Like every new vitamin, vitamin K possesses numerous methods of assay and standards of unity. For details of this subject two articles are referred to.[63] The wide interest in vitamin K and associated naphthoquinones has given rise to the need for convenient and accurate methods for their estimation. A step in this direction was made by Trenner and Bacher,[64] who described a method by which many quinone-like substances may be assayed. Others have also recently reported work in this direction.[65]

Of clinical importance are the methods by which deficiency of vitamin K can be recognized by simple laboratory procedures. Several excellent methods for measuring deficiency of prothrombin in the blood of man have been described, but in the experience of many the method developed by Quick and his associates has been found adaptable for general use in the clinical laboratory. The method developed by Warner and his associates also is used with modification in many laboratories.[65] Details of these methods are given in several publications.[66]

61. Wilder, R. M.; Browne, H. C., and Butt, H. R.: Diseases of Metabolism and Nutrition: Review of Certain Recent Contributions: I. Diseases of Metabolism; II. Nutrition, Arch. Int. Med. **65**: 390-460 (Feb.) 1940. Butt, H. R., and Leary, W. V.: Diseases of Nutrition: Review of Certain Recent Contributions, Arch. Int. Med. **67**: 411-465 (Feb.) 1941. Butt, Leary and Wilder.[73]

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63. Anshacher, S.: Editorial Review: The Bioassay of Vitamin K, J. Nutrition **21**: 1-12 (Jan.) 1941. Almquist, H. J.: Vitamin K, Physiol. Rev. **21**: 194-216 (Jan.) 1941.

64. Trenner, N. R., and Bacher, F. A.: A Quantitative Reduction-Oxidation Method for the Estimation of Vitamin K; and Associated Quinones and Naphthoquinones, J. Biol. Chem. **137**: 745-755 (Feb.) 1941.

65. Irreverre, Filadelfo, and Sullivan, M. X.: A Colorimetric Test for Vitamin K_1, Science **94**: 497-498 (Nov. 21) 1941. Scudi, J. V., and Buhs, R. P.: A Colorimetric Oxidation-Reduction Method for the Determinations of the K Vitamins, J. Biol. Chem. **141**: 451-464 (Nov.) 1941. Warner, E. D.; Brinkhous, K. M., and Smith, H. P.: A Quantitative Study on Blood Clotting: Prothrombin Fluctuations Under Experimental Conditions, Am. J. Physiol. **114**: 667-675 (Feb.) 1936.

66. Herbert, Freda K.: The Estimation of Prothrombin in Human Plasma, Biochem. J. **34**: 1554-1568 (Dec.) 1940. Souter, A. W., and Kark, Robert: Quick's Prothrombin Test Simplified by the Use of a Stable Thromboplastin, Am. J. M. Sc. **200**: 603-607 (Nov.) 1940. Quick, A. J.; Stanley-Brown, Margaret, and Bancroft, F. W.: A Study of the Coagulation Defect in Hemophilia and in Jaundice, ibid. **190**: 501-511 (Oct.) 1935. Butt and Snell.[58] Brinkhous.[59] Bay.[60] Koller.[74]

The so-called bedside method has received considerable use and is reported to be of great value for the general practitioner. Suitable compact sets for making this measurement at the bedside are now available commercially.[67] Several micromethods for measuring deficiency of prothrombin of infants also have been described and are used in many institutions routinely.[68]

It must be admitted that all current methods for the estimation of prothrombin are, of necessity, indirect. However, certain of these methods of measuring prothrombin are the most nearly accurate methods available at present for estimation of the tendency of a patient to bleed in the presence of suspected deficiency of prothrombin. The information afforded by the measurement of prothrombin in the circulating blood is much more nearly accurate in the prediction of the tendency of a patient to bleed than is the measurement of the coagulation of bleeding time as formerly used in the consideration of such tendencies.

CLINICAL USE OF VITAMIN K

Among Adults.—A number of conditions have been reported in which a deficiency of prothrombin exists that can be corrected by the administration of vitamin K.[69] Deficiency of prothrombin among human beings apparently may occur in any of the following circumstances:

1. After ingestion of a diet inadequate in vitamin K. This condition is rare but the clinical observation is well supported by the experimental production of low values for prothrombin in the blood of rabbits and mice following administration of diets deficient in vitamin K.

2. With inadequate intestinal absorption. This may result from (*a*) lack of bile in the intestine owing to decreased secretion of bile salts, (*b*) obstruction of the bile duct from any cause or (*c*) to inadequate absorption attributable to various intestinal lesions, such as intestinal obstruction, and to short-circuiting surgical procedures. It likewise has been demonstrated that severe diarrheal diseases, such as ulcerative colitis, sprue or celiac disease, may result in a deficiency of prothrombin.[70]

3. Injury to the liver. There is, of course, considerable evidence, both clinical and experimental, to indicate that the liver plays an active part in the formation of prothrombin and that any severe injury to this organ results in a deficiency of prothrombin.[71]

The story of deficiency of prothrombin resulting from obstructive jaundice or from biliary fistula has been told so often that it needs no repetition here, but the group of cases in which there is inadequate absorptive surfaces of the intestine deserves some consideration. A deficiency of prothrombin as a cause of bleeding in cases of various intestinal disorders is something new in clinical medicine. Although instances of deficiency in prothrombin referable to the effect of intestinal disorders are not often encountered, they do comprise a rather distinct group and one which bears close observation. When patients who have extensive disease of the intestine, such as sprue, chronic ulcerative colitis, intestinal obstruction or ileitis, or who have had multiple short-circuiting operations on the intestinal tract experience hemorrhage either before or after surgical treatment, deficiency in prothrombin should be recognized and corrected before other forms of treatment are instituted. One of the most important points in handling these conditions is for the physician to follow the level of prothrombin in the blood closely before and after operation in all cases of abnormalities of intestinal mucosa, particularly in cases in which the postoperative condition requires continued aspiration of gas and secretions from the intestinal tract. This practice has solved the mystery of obscure intestinal bleeding which occurs frequently in such cases and definitely has reduced postoperative morbidity and mortality.

It has been well demonstrated clinically that primary hepatic disease, such as cirrhosis, atrophy or chronic hepatitis, frequently is accompanied by deficiency of prothrombin. This deficiency of prothrombin is not the result of deficiency of vitamin K but apparently is the direct result of severe hepatic damage. Under these conditions the deficiency of prothrombin usually is not relieved by administration of vitamin K in any amount. It is well to recall that instances of severe hepatic damage occur in any disease in which the liver might be involved, and although this group of cases is somewhat small this possibility must be considered. It is true that frequently repeated doses of vitamin K are necessary in order to produce the desired effect, but when the usual therapeutic dose of vitamin K has been doubled or tripled without producing the desired effect it is fairly certain that, regardless of the amount of vitamin K administered, there will be no response to elevation of prothrombin in the circulating blood.

Regardless of the etiologic factors in the deficiency of prothrombin of man, treatment in most instances essentially is the same. In cases in which there is inadequate bile in the gastrointestinal tract natural vitamin K_1 or synthetic compounds exhibiting vitamin K activity which are given by mouth should be accompanied by administration of from 5 to 10 grains (0.3 to 0.65 Gm.) of bile salts. Synthetic compounds with vitamin K activity, now available on the market and given orally in doses of from 1 to 2 mg. daily, usually constitute an adequate dose. There also is available on the market a water soluble compound, 4-amino-2-methyl-1-naphthol hydrochloride, which can be given effectively by mouth without bile salts. This compound and other synthetic compounds also are available commercially for intravenous and intramus-

67. Ziffren, S. E.; Owen, C. A.; Hoffman, G. R., and Smith, H. P.: Control of Vitamin K Therapy: Compensatory Mechanism at Low Prothrombin Levels, Proc. Soc. Exper. Biol. & Med. **46**: 595-597 (April) 1939.

68. Kato, Katsuji: Microprothrombin Test with Capillary Whole Blood: A Modification of Quick's Quantitative Method, Am. J. Clin. Path. **10**: 147-153 (Feb.) 1940. Quick, A. J.: Determinations of Prothrombin, Proc. Soc. Exper. Biol. & Med. **42**: 788-789 (Dec.) 1939. Bray, W. E., and Kelley, O. R.: Prothrombin Studies, Especially in the Newborn, Am. J. Clin. Path. **10**: 154-167 (Feb.) 1940. Kelley, O. R., and Bray, W. E.: Prothrombin Time Determination, J. Lab. & Clin. Med. **25**: 527-530 (Feb.) 1940. Kato, Katsuji, and Poncher, H. G.: The Prothrombin in the Blood of Newborn Mature and Immature Infants as Determined by the Microprothrombin Test, J. A. M. A. **114**: 749-753 (March 2) 1940.

69. Kark, Robert, and Souter, A. W.: Hypoprothrombinaemia and Avitaminosis-K in Man, Brit. M. J. **2**: 190-194 (Aug. 9) 1941. Smith, H. P., and Owen, C. A.: Vitamin K: Its Use in Patients with Obstructive Jaundice or with Biliary Fistulas, Rev. Gastroenterol. **7**: 520-526 (Nov.-Dec.) 1940. Hicks, J. D.: A Review of the Literature Concerning Hemorrhage in Obstructive Jaundice; the Significance of Prothrombin and of Vitamin K Therapy, M. J. Australia **1**: 46-51 (Jan. 11) 1941.

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71. Butt, H. R.; Leary, W. V., and Wilder, R. M.: Diseases of Nutrition: Review of Certain Recent Contributions, Arch. Int. Med. **69**: 277-343 (Feb.) 1942.

cular administration.[72] Their action is rapid.[73] Daily doses of from 1 to 2 mg. usually are sufficient parenterally. Most investigators interested in this subject suggest that prior to operation in any of these conditions, regardless of the concentration of prothrombin in the blood, vitamin K in some form should be given for from one to two days. After operation, the concentration of prothrombin in the blood should be followed carefully and vitamin K administered as necessary. In instances in which the level of prothrombin in the circulating blood is sharply decreased before operation, vitamin K should be administered routinely preoperatively and postoperatively for several days, and the concentration of prothrombin in the blood should be determined for at least eight to ten days thereafter.

Some workers[74] recently have felt that the change effected in a particular level of prothrombin by administration of vitamin K may provide some index as to the nature of the disease being treated, with particular reference to intrahepatic and extrahepatic jaundice. Data now at hand do not unequivocally establish this fact.

Deficiency of Prothrombin Among Newborn Infants.—It is agreed generally that during the first few days of an infant's life a deficiency of prothrombin exists in the circulating blood. The cause of this normal physiologic deficiency, however, is still controversial. Waddell and Guerry were the first to report the important discovery that this physiologic deficiency of prothrombin of newborn infants and the bleeding tendency which sometimes developed could be corrected by administration of vitamin K. Since that time numerous reports have appeared concerning the effect of the various compounds possessing vitamin K activity on the level of prothrombin of newborn infants and the effect of such compounds on the hemorrhage which frequently occurs. The important suggestion also has been made that the deficiency of prothrombin existing at the time of birth might account in many instances for the intracranial hemorrhages which sometimes follow protracted labor and which frequently result in permanent paralysis.

It has been reported and well established by several groups of workers that administration of vitamin K to mothers prior to delivery will prevent the usual fall in the level of prothrombin in the blood which is observed among newborn infants and that administration of vitamin K to the newborn infant also will increase concentration of prothrombin in the plasma.[75]

On the basis of work now available, it appears that 2 mg. of menadione given by mouth to a mother one half to forty-eight hours before delivery is effective in preventing hemorrhagic disease of the newborn infant.[76] There is good evidence to indicate that, although the feeding of vitamin K to the infant after birth increases the concentration of prothrombin, the concentrations in these instances are not as high as those achieved by antepartum administration of the vitamin to the mother.

Many workers believe that instances of cerebral hemorrhage occurring in the course of birth with minimal trauma are precipitated by small hemorrhages which endure for a number of days. For this reason many workers interested in this problem believe that the lives of some of the infants might be saved if the blood at birth exhibits better properties of coagulation. Most investigators believe that vitamin K given in some form should be administered to every mother at the onset of labor. Some still insist that the vitamin should also be given to the newborn infant as an added precaution. In any event, the plan is so simple, the vitamin so cheap and the toxic reactions so minimal that this program should be adopted universally in the hope of preventing injury at birth.

72. Olwin, J. H.: The Intravenous Use of Vitamin K, J. A. M. A. **117**: 432-435 (Aug. 9) 1941. Emmett, A. D.; Kamm, Oliver, and Sharp, E. A.: The Vitamin K Activity of 4-Amino-2-Methyl-1-Naphthol and 4-Amino-3-Methyl-1-Napthol, J. Biol. Chem. **138**: 285-286 (March) 1940. Anderson, E. R.; Karabin, J. E.; Udesky, Herbert, and Seed, Lindon: Parenteral Administration of a Water-Soluble Compound with Vitamin K Activity: 4-Amino-2-Methyl-1-Naphthol Hydrochloride, Arch. Surg. **41**: 1244-1250 (Nov.) 1940.

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74. Allen, J. G., and Julian, O. C.: Response of Plasma Prothrombin to Vitamin K Substitute Therapy in Cases of Hepatic Disease, Arch. Surg. **41**: 1363-1365 (Dec.) 1940. Andrus, W. DeW.: The Newer Knowledge of Vitamin K, Bull. New York Acad. Med. **17**: 116-134 (Feb.) 1941.

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Council on Pharmacy and Chemistry

NEW AND NONOFFICIAL REMEDIES

THE FOLLOWING ADDITIONAL ARTICLES HAVE BEEN ACCEPTED AS CONFORMING TO THE RULES OF THE COUNCIL ON PHARMACY AND CHEMISTRY OF THE AMERICAN MEDICAL ASSOCIATION FOR ADMISSION TO NEW AND NONOFFICIAL REMEDIES. A COPY OF THE RULES ON WHICH THE COUNCIL BASES ITS ACTION WILL BE SENT ON APPLICATION.

AUSTIN E. SMITH, M.D., Acting Secretary.

ISOTONIC SOLUTION OF THREE CHLORIDES (See New and Nonofficial Remedies, 1942, p. 427).

The following dosage form has been accepted:

THE UPJOHN COMPANY, KALAMAZOO, MICH.

Ringer's Solution: 500 cc. and 1,000 cc. Upjohn Infusion Bottles. Each hundred cubic centimeters contains 0.7 Gm. of sodium chloride-U. S. P., 0.03 Gm. of potassium chloride-N. F. and 0.025 Gm. of calcium chloride-U. S. P.

SULFATHIAZOLE (See New and Nonofficial Remedies, 1942, p. 150).

The following dosage form has been accepted:

E. S. MILLER LABORATORIES, INC., LOS ANGELES.

Tablets Sulfathiazole: 0.5 Gm. (7.7 grains).

THIAMINE HYDROCHLORIDE (See New and Nonofficial Remedies, 1942, p. 555).

The following dosage forms have been accepted:

THE LAKESIDE LABORATORIES, INC., MILWAUKEE.

Tablets Thiamine Hydrochloride: 1 mg., 3 mg., 5 mg.

Ampul Solution Thiamine Hydrochloride, 10 mg. per cc.: 1 cc. Preserved with 0.5 per cent of chlorobutanol.

Solution Thiamine Hydrochloride, 10 mg. per cc.: 15 cc. vial. Preserved with 0.5 per cent of chlorobutanol.

Ampul Solution Thiamine Hydrochloride, 25 mg. per cc.: 1 cc. Preserved with 0.5 per cent of chlorobutanol.

Solution Thiamine Hydrochloride, 25 mg. per cc.: 15 cc. vial. Preserved with 0.5 per cent of chlorobutanol.

Ampul Solution Thiamine Hydrochloride, 50 mg. per cc.: 1 cc. Preserved with 0.5 per cent of chlorobutanol.

Solution Thiamine Hydrochloride, 50 mg. per cc.: 15 cc. and 50 cc. vials. Preserved with 0.5 per cent of chlorobutanol.

Solution Thiamine Hydrochloride, 150 mg. per cc.: 5 cc. vial. Preserved with 0.5 per cent of chlorobutanol.

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SATURDAY, NOVEMBER 28, 1942

ANTIPROTHROMBIN THERAPY

Elsewhere in this issue appears a series of four papers on the development of dicoumarin as a substance definitely concerned with the mechanism of coagulation of the blood. The record of the development of this product is one of the most dramatic stories in the field of chemotherapy. In brief, the observation of a peculiar disease occurring in animals led to an investigation of the nature of its causation and then to an effort to apply the product producing the disease to a useful purpose in the control of the physiology of the human being.

Cattlemen of the Middle West have long been familiar with the toxic effects of improperly cured hay or silage. One type of hay intoxication was studied in detail about twenty years ago by Schofield [1] of Canada and Roderick [2] of North Dakota. This syndrome was observed in cattle, sheep or rabbits fed on spoiled sweet clover (Melilotus alba or Melilotus officinalis) and was therefore named "sweet clover disease." The disease is characterized by an almost complete loss of the clotting power of the blood with resultant multiple hemorrhages in internal organs and tissue. In its earlier stage the disease can be cured by eliminating spoiled sweet clover from the daily diet plus massive blood or serum transfusion from normal animals. If not thus treated, however, the "hemorrhagic sweet clover disease" usually proves fatal.

Roderick,[3] Quick [4] and others showed that the reduced clotting power of the blood is due to destruction or inactivation of prothrombin. After a decade of repeated failures Roberts,[5] Campbell [6] and others succeeded in extracting the toxic agent from spoiled sweet clover. From such extracts they obtained a crystalline material with the empirical formula $C_{19}H_{12}O_6$ (melting point 288-289 C.). This product was two hundred times more toxic than the original spoiled hay, from which they concluded that spoiled sweet clover contains approximately 0.03 mg. per gram of the active toxic factor.

Detailed chemical analyses with artificial synthesis of this toxic agent were subsequently made by Stahmann and his colleagues [7] of the University of Wisconsin. The Wisconsin chemists conclude that the substance is 3,3'-methylene-bis-(4-hydroxycoumarin). Tested on rabbits, their synthetic product and the natural toxin were of identical toxic and antiprothrombic titers. Stimulated by an anticipated research interest in this anticoagulant, 3,3'-methylene-bis has been made commercially available by Swedish biochemists and offered under the nonproprietary name AP (antiprothrombin).

Lehmann [8] found that in rabbits the lethal dose of this commercial product is 250 mg. per kilogram of body weight. Death is apparently due to kidney injury. The substance, however, can be given by mouth in doses of 3 to 4 mg. per kilogram of body weight without demonstrable toxic effects. One 4 mg. oral dose causes an 80 per cent fall in prothrombin index within twenty-four hours. Daily repetition of this dose for twenty days causes a further lowering of the prothrombin titer to about 10 per cent of normal. This prolonged daily administration also is without demonstrable deleterious effects. Similar results were previously reported by Overman.[9] Lehmann further showed that the substance is apparently nonantigenic for rabbits, since they do not acquire demonstrable immunity to its subsequent administration.

Encouraged by these experimental data, Lehmann began therapeutic tests on man. The Swedish clinician found that when 0.25 to 1 Gm. of AP is given by mouth a fall in prothrombin index occurs in man similar to that produced in lower animals. This fall is usually without concomitant toxic effects. In a few cases mild nausea or diarrhea was observed after the first dose but not after subsequent administrations. Thus far 17 cases of thrombosis have been treated with this anticoagulant. In each case the resulting fall in prothrombin titer was accompanied by clinical improvement, as shown by a fall in temperature and diminished turgor of the leg. In all cases of phlegmasia alba dolens the course of the disease was shortened and increase in the thrombosis did not occur after the beginning of AP administration. Oral administration of AP for the prevention of postoperative thrombosis is now under investigation.

Whether or not administration of AP hastens the liquefaction or absorption of previously formed thrombi

1. Schofield, F. S.: Canad. Vet. Rec. **3**: 74, 1922.
2. Roderick, L. M.: J. Am. Vet. M. A. **74**: 314, 1929.
3. Roderick, L. M.: Am. J. Physiol. **96**: 413 (Feb.) 1931.
4. Quick, A. J.: Am. J. Physiol. **118**: 260 (Feb.) 1937.
5. Roberts, W. L.: Summaries of Doctorate Dissertations, Madison, Wis. **10**: 501, 1935.
6. Campbell, H. A., and Link, K. P.: J. Biol. Chem. **138**: 21 (March) 1941.
7. Stahmann, M. A.; Huebner, C. F., and Link, K. P.: J. Biol. Chem. **138**: 513 (April) 1941.
8. Lehmann, Jörgen: Science **96**: 345 (Oct. 9) 1942.
9. Overman, R. S.; Stahmann, M. A.; Sullivan, W. R.; Huebner, C. F.; Campbell, H. A., and Link, K. P.: J. Biol. Chem. **143**: 941 (Feb.) 1942.

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or fibrin deposits has not yet been determined. Meanwhile American botanists have become interested in the sweet clover toxin. Brink [10] and others, for example, are speculating on the possibility of finding or developing varieties of sweet clover relatively free from coumarin, the basic plant component from which the toxic agent is formed during spoilage.

HUMAN ALBUMIN IN MILITARY MEDICINE

Albumin makes up about 62 per cent of the total protein of human plasma and is chemically the most soluble and most stable of the plasma proteins. Its smaller molecular weight and greater net charge render it more important than globulin in maintaining the colloid osmotic pressure of the plasma. This pressure is the principal force counteracting filtration pressure; hence albumin plays a major part in maintaining the volume of fluid in the blood stream. Because of its molecular symmetry, albumin makes a less viscous solution than the other proteins and therefore can be readily injected in concentrations of 25 per cent. The advantage of plasma over solutions of salt and dextrose in the treatment of shock depends on the osmotic pressure exerted by its proteins (chiefly albumin), which keeps fluid in the circulation at a time when protein is being lost faster than it can be synthesized. Hence, in the emergency treatment of shock, albumin offers distinct practical advantages because it is stable, compact and ready for instant use.

Because the urgent demands of treatment in clinical cases of shock preclude detailed study, Heyl and Janeway [1] attempted to evaluate the physiologic effect of human albumin solutions in man under carefully controlled conditions of a blood volume depleted by venesection. The plasma volume was first determined in normal subjects. Immediately thereafter a rapid venesection of approximately 15 per cent of the blood volume was performed, the amount withdrawn being carefully measured. The injection of concentrated (25 per cent) albumin was begun at once. One hour later the plasma volume was again determined, and the trend of plasma volume was followed by frequent determinations of the values for hemoglobin, hematocrit reading and total protein. The results of these quantitative observations showed that concentrated human albumin will rapidly augment the plasma volume by drawing fluid into the circulation. Furthermore, calculations from these experimental data indicated that each gram of injected albumin (dose, 30 to 35 Gm.) is capable of adding 14 to 24 cc. of fluid to the plasma, with an average in 9 subjects of 18 cc. at one hour after injection. This result, Heyl and Janeway say, confirms in vitro studies of osmotic pressure which form the basis for the standard albumin unit of 25 Gm., which is therefore equivalent to about 450 cc. of circulating plasma or 500 cc. of citrated plasma.

Evidence that human albumin is safe and effective under clinical conditions is supplied by Woodruff and Gibson,[2] who report the effects noted in 200 instances in which albumin was given. Fifty-one were tests for reactions and eight were experiments, while the remainder were therapeutic injections in clinical cases. The albumin used in the study was prepared under the direction of Dr. E. J. Cohn of the department of physical chemistry at Harvard Medical School by methods developed in the Harvard plasma fractionation laboratory. The types of cases treated were classified as shock due to trauma, hemorrhage, operation and infection, early and late burns, hypoproteinemia, experimental cases and miscellaneous conditions. The twenty-one preparations released for clinical use gave almost no reactions when tested in 48 cases. Among the 141 cases in which clinical treatment with albumin was given there were nine fairly definite reactions. Five of these were merely flushing or slight lumbar pain, while four were severe chills or fall in blood pressure. Albumin produced prompt recovery in most cases of surgical shock. Rapid and pronounced hemodilution was shown to occur. One unit of concentrated human albumin (100 cc. 25 per cent solution) was used as the initial dose in shock, repeated in fifteen to thirty minutes if necessary. Further, these investigations showed that protein loss in burns can be replaced and the hemoconcentration prevented or corrected. In severe injuries and shock, transfusions of whole blood or intravenous saline solution enhance the effect. When intravenous fluids are given, they should contain at least 2 units of albumin per liter. The initial dose for burns is 1 or more units, depending on the extent of the burn. Subsequent doses should be regulated so as to prevent definite hemoconcentration and should be given in the ratio of 2 units of albumin per liter of solution.

The administration of human serum albumin may be considered an established procedure on the basis of this work and the work which has preceded it. The third paper of this series, by Newhouser and Lozner,[3] describes the standard Army-Navy package of serum albumin human (concentrated). For this purpose a "unit" of human serum albumin is defined as 25 Gm. This is osmotically equivalent to approximately 500 cc. of citrated plasma. In the standard package the 25 Gm. is dissolved in 100 cc. of buffered diluent, in which concentration it is stable for temperatures up to 50 C. The solution is contained in a double ended glass ampule, rubber stoppered at each end. Each ampule

10. Brink, R. A., and Roberts, W. L.: Science **86**: 41 (July 9) 1937.
1. Heyl, J. T., and Janeway, C. A.: The Use of Human Albumin in Military Medicine, U. S. Nav. M. Bull. **40**: 785 (Oct.) 1942.
2. Woodruff, L. M., and Gibson, S. T.: The Clinical Evaluation of Human Albumin, U. S. Nav. M. Bull. **40**: 791 (Oct.) 1942.
3. Newhouser, L. R., and Lozner, E. L.: The Standard Army-Navy Package of Serum Albumin Human, U. S. Nav. M. Bull. **40**: 796 (Oct.) 1942.

together with the apparatus for its administration is enclosed in a metal can. Three of these cans, containing the osmotic equivalent of 1,500 cc. of citrated plasma, are packaged in a fiber board box.

Because of this and previous work, a new method of great effectiveness has been made available for combating shock, hemorrhage and burns. Furthermore, this series of investigations may be recognized as a demonstration of cooperative research at its best.

Current Comment

PREMEDICAL EDUCATION AND THE EIGHTEEN YEAR OLD DRAFTEE

In an address before the Congress on Medical Education and Licensure in 1939 President J. B. Conant of Harvard University called attention to the fact that the total professional training of medical men depended to some extent on their plans for the future. Those contemplating research as a career would require much more of the fundamental sciences than would those who are looking forward to general practice. The exigencies of war have already demonstrated the possibility of serious modifications of technics and practices which in times of peace seem unalterable. The acceleration of medical education and the proposed changes in licensure are examples. In 1939 President Conant made the following suggestions:

> Encourage college freshmen who are looking forward to a medical career to apply for admission to a medical school three years in advance. Let the admission committee base its rejection or conditional acceptance of such applications on the school record, on the first year college record and on performance in such tests as the scholastic aptitude test. After the undergraduate in question has been tentatively enrolled as a future medical school student, let there be cooperation between the medical school and the college in working out through a joint committee an intelligent college program for the remaining three years.

This proposal by President Conant, it has been suggested, may be part of the answer to the maintenance of an adequate number of properly qualified young men in the field of premedical and medical education during the present emergency. The average age of young men at graduation from high school is 17.2 years. If they are enrolled in college before they are 18 years of age they might be deferred by selective service boards until they have completed the session in which they are enrolled. Under the plan proposed by President Conant of Harvard they could be matriculated in the medical school after the completion of the first year of premedical education and would thus be made immediately available for the reserve of the Army or Navy medical departments. Obviously young men who could not pass the physical examination for such reserves might have to be considered in some different manner. The proposal by President Conant is supplemented by his suggestion that the old concept of four years of scientific and liberal education, followed by four years of professional training, be replaced by a system in which the whole eight years is regarded as a unit to provide a balanced intellectual diet suited to each student's talents and interests.

A HEMOPHILIA-LIKE DISEASE IN SWINE

Animal maladies which are similar to those encountered clinically in man are of special interest because the probability of developing therapeutic measures a clinical condition is enhanced when a similar situation can be studied experimentally in animals. A hemophilia-like disease has been found in swine. The condition first attracted the attention of Hogan and his co-workers,[1] who noted that a number of hogs in the Missouri Agricultural Experiment Station herd possessed a defective blood clotting mechanism. Many of the animals have died from hemorrhage, either spontaneous or as the result of minor wounds. The bleeders are progeny of an inbreeding investigation, and the affected animals are closely related. Recently the characteristics of the disease were described[2]; just as in clinical hemophilia, the bleeding time by Duke's method[3] is normal. If an incision of any extent is made, however, the bleeding time is prolonged indefinitely. A 1 cm. slit in the edge of a defective swine's ear, for instance, may result in death. Examination of the blood of affected animals shows normal concentrations of prothrombin, calcium and fibrinogen. There is a deficiency of readily available thromboplastin, however, and the whole blood coagulation time is greatly extended. The platelets, though normal in number, are abnormally stable. The differential diagnosis of hemophilia from other hemorrhagic diseases has been carefully studied by Quick,[4] who has outlined a diagnostic procedure which includes observations on the coagulation time of the blood and of recalcified oxalated plasma, as well as on clot retraction, bleeding time and prothrombin level. The application of Quick's method to bleeders and normal swine shows that the characteristics of the porcine disease fit closely the criteria set up for the diagnosis of hemophilia. Indeed, the disease does not differ in any significant way from human hemophilia, except that in swine the defect is not sex linked. Both male and female swine are subject to the bleeding disease, and both sexes may transmit it.

SENATOR EUGENE D. MILLIKIN, COLORADO, SPEAKS FOR THE RECORD

On November 16 Senator Eugene D. Millikin of Colorado, a member of the subcommittee of the Senate Committee on Education and Labor, which is holding hearings on medical manpower, made the following statement for the record:

> I would like to say if there is anything in the record that indicates any criticism on the part of this Committee of the physicians generally or of the American Medical Association, I should like to dissociate myself from that criticism. I repeat that a transcript should be furnished to the American Medical Association, so that they may reply to anything that they feel is critical of them.

1. Hogan, A. G.; Muhrer, M. E., and Bogart, R.: A Hemophilia-like Disease in Swine, Proc. Soc. Exper. Biol. & Med. **48**:217 (Oct.) 1941.
2. Muhrer, M. E.; Hogan, A. G., and Bogart, R.: A Defect in the Coagulation Mechanism of Swine Blood, Am. J. Physiol. **136**:355 (May) 1942.
3. Duke, W. W.: The Relation of Blood Platelets of Hemorrhagic Disease: Description of a Method for Determining the Bleeding Time and Coagulation Time and Report of Three Cases of Hemorrhagic Disease Relieved by Transfusion, J. A. M. A. **55**:1185 (Oct.) 1910.
4. Quick, A. J.: The Diagnosis of Hemophilia, Am. J. M. Sc. **201**:469 (April) 1941.

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MEDICINE AND THE WAR

In this section of The Journal each week will appear official notices by the Committee on War Participation of the American Medical Association, announcements by the Surgeon Generals of the Army, Navy and Public Health Service, and other governmental agencies dealing with medicine and the war and such other information and announcements as will be useful to the medical profession.

THE CRITICAL ANTIMALARIAL PROBLEM AND ITS SOLUTION

It is axiomatic that troops cannot operate successfully in endemic malarial areas without an effective antimalarial drug. Malaria is present throughout most of the tropical and subtropical world. The extent of operations in these regions is steadily increasing and it is conceivable that they may grow to tremendous proportions within a short time.

Ninety per cent of the world's customary sources of quinine was cut off when the Japanese invaded Java and the Philippines. India has in the past frequently imported cinchona bark from Java to bolster her supply. South America has for many years been importing bark from Java for domestic use.

What measures should be taken to safeguard our limited stocks? Early in May the War Production Board recognized the critical nature of the problem. In order to avail itself of medical advice it asked the National Research Council to form a committee on drugs and medical supplies to investigate and advise not only on the many problems which the quinine scarcity presented but also on any other matters pertaining to drugs and medical supplies which concerned the War Production Board. This committee has two subcommittees, one on essential drugs, the other on hospital and surgical supplies. The committee has also used the advice of other National Research Council committees, such as the Subcommittee on Tropical Diseases, for answers to specific problems in the therapy of malaria, and the Committee on Surgery for technical problems related to surgical supplies.

The program worked out by the joint efforts of the War Production Board and the National Research Council progressed as follows:

1. The War Production Board issued "Quinine Order M-131," which froze present stocks and restricted the use of quinine and other cinchona alkaloids to the treatment of malaria, except that quinidine could also be used for the treatment of cardiac disorders. Requests for quinine for the treatment of various other conditions, including quinine urethane and quinine urea as local anesthetics, quinine in sodium morrhuate for varicose vein injections, quinine salts for induction of labor, quinine salts in the treatment of night cramps, multiple sclerosis, amyotrophic lateral sclerosis, myotonia atrophica, paralysis agitans and myotonia congenita, have all been carefully considered and denied with the exception of the use of quinine in the treatment of myotonia congenita.

2. Repeated persuasive efforts in the trade press have been instituted by the War Production Board to bring in all unopened packages of quinine, and now the machinery is being set up for bringing in opened packages, analyzing each and pooling according to the type of preparation.

3. To effect the maximum antimalarial value of available cinchona bark from South America, the National Research Council undertook to investigate the feasibility of substituting totaquine for quinine in the treatment of malaria. Totaquine had been recognized previously by the U. S. Pharmacopeia and a standard set, which appears in the twelfth edition. This standard seemed to allow for too much latitude both in quinine content and in total crystallizable alkaloid content. Accordingly, the National Research Council asked the U. S. Pharmacopeia to revise the monograph to obtain a more uniform standard. As the result the U. S. Pharmacopeia adopted the following monograph, which will appear in a supplement of the twelfth edition:

> "Totaquine is a mixture of alkaloids from the bark of Cinchona succirubra Pavon and other suitable species of Cinchona. It contains not less than 7 per cent and not more than 12 per cent of anhydrous quinine, and a total of not less than 70 per cent and not more than 80 per cent of the anhydrous crystallizable cinchona alkaloids, the designation "crystallizable alkaloids" referring to cinchonidine, cinchonine, quinidine and quinine.
>
> "Totaquine of a higher quinine percentage may be reduced to the official quinine standard by a mixture with totaquine of a lower percentage or with any of the diluents permitted for powdered extracts under Extracta, page 174, provided the total anhydrous crystallizable cinchona alkaloids do not fall below the required percentage.
>
> "The U. S. Pharmacopeia on the advice of the National Research Council recommended the dose to be 10 grains three times a day for seven days."

It was the considered opinion of the Subcommittee on Tropical Diseases and the Committee on Medicine of the National Research Council that in this dosage totaquine should prove to be as effective as quinine sulfate in the oral treatment of malaria. A satisfactory price structure has been set up for cinchona bark from South America by the Board of Economic Warfare, and every effort is being made to stimulate importation.

4. The production of atabrine has been stimulated by the War Production Board, and the present outlook on production sufficient to supply all anticipated needs is practically assured. Extensive chemical, pharmacologic and clinical investigations have been conducted by various groups of the National Research Council working under grants by the Office of Scientific Research and Development. The chemical studies have adequately demonstrated the chemical purity of the atabrine produced in this country. Pharmacologic and clinical investigations have revealed temporary gastrointestinal disturbances in a variable percentage of persons receiving atabrine in the suppressive (prophylactic) treatment of malaria. Further study is under way to elucidate the cause and remove if possible these disturbances. There is a tendency to the development of a yellow pigmentation of the skin during administration which disappears after the drug is stopped. This is harmless and not associated with any disturbance in liver function.

5. Experience with the use of atabrine by the British, both therapeutically and as a suppressive, indicates that it is an effective antimalarial and in some ways superior to quinine. It is slower in action and therefore not as useful in the initial treatment of malaria, but after one to three days of quinine therapy atabrine is exceedingly effective. At a recent meeting of the Subcommittee on Tropical Diseases of the National Research Council, the following program of dosage was endorsed as an efficient routine of therapy:

(1) *Combined QAP Treatment* (method of choice).

- (*a*) Totaquine or Quinine sulfate 0.64 Gm. (10 grains) three times daily after meals for two or three days or until pyrexia is controlled. Then give
- (*b*) Atabrine 0.1 Gm. (1½ grains) three times daily after meals for five days. Then after two days without antimalarial medication give
- (*c*) Plasmochin 0.01 Gm. ($\frac{3}{20}$ grain) three times daily after meals for five days, except for the debilitated patient, who should receive only two doses daily. (Discontinue if toxic symptoms occur. Never give atabrine and plasmochin concurrently.)

(2) *Atabrine-Plasmochin Treatment* (may be used for simple vivax infections and in other infections when no totaquine or quinine is available).

(*a*) Atabrine, as above for seven days. Then, after two days without antimalarial medication give plasmochin 0.01 Gm. three times daily for five days, as above.

(3) *Totaquine or Quinine-Plasmochin Treatment* (method when no atabrine is available).

(*a*) Totaquine or quinine sulfate, as above, for seven days, during the last five of which accompany each dose of totaquine or quinine with plasmochin 0.01 Gm. three times daily.

(4) *Suppressive Treatment.*

(*a*) Atabrine. Give 0.1 Gm. (1½ grains) twice daily after meals on two days a week, allowing a two or three days interval between days of medication.

It was the consensus of this subcommittee that until we have had more experience with the use of atabrine it should be used only under the guidance of a physician or public health officer.

6. Government stockpiles have been recommended not only for quinine but for the other alkaloids (cinchonine, cinchonidine and quinidine) and totaquine, and the Defense Supplies Corporation is purchasing against these stockpile recommendations.

It is anticipated on the basis of recent investigations by the Board of Economic Warfare that the barks from South America of low quinine content but sufficiently rich in total crystallizable alkaloids (quinine, quinidine, cinchonine, cinchonidine) to make totaquine of U. S. P. standards will be found in sufficient quantity to enable totaquine to replace civilian quinine requirements. The amount of this bark which is available has been an unknown factor, because its low quinine content has not made it previously marketable.

If every physician in civilian practice and every public health officer will follow the recommendations of the Subcommittee on Tropical Diseases regarding the use of atabrine and will use totaquine in place of quinine whenever totaquine is available, an important and material conservation in our limited stocks of quinine will be accomplished.

LEWIS H. WEED, M.D.
Chairman, Division of Medical Sciences, National Research Council.

ARMY

COMMISSION TO STUDY TYPHUS IN WAR ZONES

The War Department and the Navy Department on November 19 announced organization of the United States of America Typhus Commission, composed of four typhus research specialists under the direction of Rear Admiral Charles S. Stephenson, Medical Corps, U. S. Navy. The commission will aid in the prevention and control of typhus among the military forces of the United Nations and civilians in war areas throughout the world. Other members of the commission are Lieut. Col. Harry Plotz, Medical Corps, Army of the United States; Senior Surgeon Adolph Rumreich, U. S. Public Health Service, and Major John C. Snyder, Medical Corps, Army of the United States.

Admiral Stephenson is a veteran with twenty-nine years' service in the Navy Medical Corps. He is director of the Division of Preventive Medicine, Bureau of Medicine and Surgery, Navy Department, and his nomination for the grade of rear admiral was recently confirmed by the Senate. He will serve in that grade until the work of the Typhus Commission is completed.

The entire commission will be militarized so that its members will be able to enter theaters of war operations throughout the world.

The commission will function as a board of strategy against typhus and will coordinate the efforts of the military, the government and the civilian in the fight against typhus. The primary purpose of the commission will be to develop information on which to base specific recommendations for the protection of our armed forces. Information so obtained will have a direct bearing on the protection of the civilian population of the United States against the introduction of typhus fever.

More than two years ago there was developed in the Office of the Surgeon General of the Army an organization known as the Division of Medical Intelligence. This organization, headed by Lieut. Col. Thomas Whayne, collects information concerning the prevalence of disease in foreign countries. The data thus collected concerning typhus show that in parts of the world a steady increase in the incidence of typhus within the last year has occurred.

Operating in areas where typhus is endemic, the commission will investigate factors which cause the spread of the disease. Liaison will be established between the commission and the government and military organizations of countries in which the commission will operate.

Heretofore the main reliance in the control of typhus has been on delousing the population. United States troops which enter endemic typhus areas are equipped with delousing equipment but the method is cumbersome. At present three vaccines are available in the United States which give a high degree of protection to animals. These vaccines have not been proved on human populations because the United States has no typhus in an epidemic form. One of these vaccines is made from infected lice, another from the lungs of infected mice and rats, and the other from the infected yolk sacs of developing chick eggs. Insecticides have been developed which have been effective in laboratory experiments and only need to be given field trials. Research has been done in the field of insect repellents; however, there is a need to try these repellents and disinfectants under natural rather than under artificial conditions.

Admiral Stephenson said the job of this commission is vital for typhus can wreck any military operation, no matter how well planned.

Colonel Plotz said the army has a special laboratory where methods of preparing typhus vaccines are being actively studied and important progress has been made. His laboratory in the Pasteur Institute in Paris, where he was engaged in typhus research from 1921 until 1939, is in the hands of the Germans. Colonel Plotz was born in New Jersey and received his M.D. degree from the College of Physicians and Surgeons, Columbia University, New York. In 1914 he was invited by the government of Serbia to study a typhus epidemic there. In 1919 and 1920 he was in Poland investigating typhus. In 1921 he entered the Pasteur Institute in Paris, where he remained until 1939. He has been in the Army of the United States since 1940.

CHEMICAL WARFARE SCHOOL

A training school for physicians in western Pennsylvania in the medical aspects of chemical warfare was opened at the Mellon Institute, Pittsburgh, November 2, to be held on four consecutive Mondays. The program was carried out under the auspices of the Allegheny County Council of Civilian Defense and the committee on postgraduate education of the Allegheny County Medical Society. T. K. T. Kruse, Ph.D., Pittsburgh, lectured, November 2, on "Pharmacology of Chemical Warfare Agents: Collective Decontamination." Dr. Irwin M. Pochapin, Pittsburgh, spoke, November 9, on "Scope and Purpose of Chemical Warfare: Classification of Chemical Warfare Agents." Dr. Pochapin also spoke, November 16, on "Treatment of Chemical Agent Casualties: Individual Protection of Technical Personnel and of the Civilian Population." On November 23 he will speak on "Treatment of Chemical Warfare Casualties: Demonstrations; Essential Supplies for First Aid."

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Dr. Rumreich was born in North Dakota. He received his M.D. degree in 1920 from the Washington University School of Medicine, St. Louis, and was commissioned in the Regular Corps of the Public Health Service in 1924. While on duty in the National Institute of Health, he conducted investigations of typhus fever and Rocky Mountain spotted fever. In 1935 Dr. Rumreich was assigned to the United States embassy in Moscow. He investigated typhus fever in Russia.

Major John Crayton Snyder was born in Salt Lake City and graduated from the Harvard Medical School. He became a staff member of the International Health Division, Rockefeller Foundation, and in 1941 went to Spain to study a typhus epidemic there. Major Snyder is a consultant to the Secretary of War on epidemic diseases and a member of the Commission on Tropical Diseases of the Board for Investigation and Control of Influenza and Other Epidemic Diseases in the Army.

GREENBRIER HOTEL CONVERTED INTO ARMY HOSPITAL

The Greenbrier Hotel and all facilities and grounds owned by the White Sulphur Springs, Inc., at White Sulphur Springs, W. Va., was acquired by the War Department on September 29 for conversion into a 2,000 bed army general hospital. The hospital will be named general hospital, but the name has not been chosen to date.

Col. Clyde M. Beck, M. C., U. S. Army, has assumed his post as commanding officer and Lieut. Col. Sam F. Seeley, M. C., U. S. Army, has been named as executive officer. No other medical corps officers have reported for duty to date, although several administrative group officers are now on duty.

Colonel Beck was transferred from Camp Joseph T. Robinson, Arkansas, where he served as commanding officer of the station hospital for nearly two years. Colonel Seeley was transferred from Washington, D. C., where as executive officer of the Procurement and Assignment Office he had been on duty for the past year.

PUEBLO'S HOSPITAL UNIT ACTIVATED

The 64th Surgical Hospital Unit, sponsored by St. Mary's Hospital, Pueblo, Colo., was recently activated at Fort Ord, California, and later went on extended maneuvers. The medical officers of the unit had been called to active duty during the early part of 1942 but later were assembled and activated as a unit. The director of the unit is Major Paul M. Ireland; other medical officers serving with the unit at the time of the report in the November issue of the *Rocky Mountain Medical Journal* are Lieut. James S. Norman, Major Paul M. Ireland, Major Albert M. Tipple, Major Merril W. Michels, Major Robert Sterling, Major Edwin W. Varley Jr., Capt. Hiram E. Armstrong, Capt. Francis S. Adams, Capt. Arnold S. Niemeyer, Capt. John Mihalick, Colorado Springs; Capt. Harold J. Beck, Capt. George C. Christie, Canon City; Capt. Eugene F. Pfile, Trinidad; Capt. Ward C. Fenton, Rocky Ford; Capt. Richard H. McIlroy, Capt. Irvin I. Schatz, Capt. Alton S. Hansen, La Junto; 1st Lieut. William N. Baker, 1st Lieut. Raymond A. Nethery, 1st Lieut. Carl W. Swartz, 1st Lieut. Roy A. L. Swanson, 1st Lieut. Walter S. Johnston. All of these officers are from Pueblo, except those whose home address is indicated.

THE SURGEON GENERAL'S OFFICE

The Surgeon General of the Army, Major Gen. James C. Magee, in an address before the Association of Military Surgeons at San Antonio, Texas, in November, is reported to have said that newly developed mobile pack equipment for the transportation of supplies for a battalion aid station is now being tested and if approved it will free medical personnel from restrictions imposed by the use of wheeled vehicles which the present load of equipment necessitates. General Magee also told of the development of an operating unit for use with armored forces in the field which consists of a van type bus of the six wheel variety which can be quickly moved and is always ready to begin operations immediately on arrival at the desired place.

The War Department has announced the appointment of Mr. Edward Reynolds, New York, as special assistant to the Surgeon General to have supervision of the nonprofessional functions of the Surgeon General's Office relating primarily to the procurement of medical supplies. Mr. Reynolds graduated from Harvard University in 1915, served as an officer in the Navy in the first world war and has been president of the Columbia Gas and Electric Corporation.

CLASS OF AVIATION PHYSIOLOGISTS

Another class of aviation physiologists was graduated at the School of Aviation Medicine, Randolph Field, Texas, October 24. The certificates of graduation were presented by Lieut. Col. Victor A. Byrnes, M. C., U. S. Army. The course in aviation physiology covers the effects of lowered barometric pressure on personnel, the operation of low pressure chambers, the effect of flight on man, the theory and practical use of oxygen equipment and the conduct of high altitude indoctrination and classification. The graduates comprised both officers and enlisted men of the medical corps and aviation corps; among the former were 1st Lieuts. Richard Bentley Baker, George J. Pastorius, Clark K. Sleeth and Charles Bruce Taylor.

SHORTEN COURSE FOR ARMY DIETITIANS

The War Department announced in November that more than two hundred dietitians will be trained each year for service at army hospitals at home and abroad. The course of training will comprise a six month pretraining course at civilian hospitals and a six month course at army hospitals. The first group of dietitians was expected to proceed to army hospitals on December 1.

CIVILIAN DEFENSE

LESSONS FROM BRITISH EXPERIENCE IN CIVILIAN DEFENSE

GEORGE BAEHR, M.D.
Office of Civilian Defense

Three years of British experience with air raids have significantly modified earlier concepts regarding the field casualty services. The following observations made on a recent inspection of emergency medical facilities in England and Scotland are forwarded for the information of regional medical officers and for transmission through state chiefs to local chiefs of emergency medical services:

1. Heavy raids occur invariably at night; heavier high explosive bombs and land mines are now being employed up to 2,000 Kg., with much greater destructive effects. Incendiary bombs are used in much larger numbers and fire is now the most serious hazard. Daylight raids are usually hit and run affairs in which solitary planes participate.

2. In large cities the field casualty services may handle 2,500 to 3,500 casualties during a night raid. All serious casualties are moved directly to hospitals, never to first aid posts. Heavy raids are apt to be repeated on subsequent nights when the protective forces are exhausted.

3. A large fleet of four stretcher ambulances is essential for life saving. Fourteen thousand ambulances were made in England and Scotland by purchasing used cars, stripping them and then mounting a simple ambulance body on the chassis. London uses over fifteen hundred of such ambulances and five hundred and fifty sitting case cars. The use of tradesmen's trucks proved universally unsatisfactory; three out of four never arrived on the scene and lives were lost as the result of the delay and confusion. Because of the large number of casualties to be transported in a few hours, no ambulances which carry less than four stretchers are employed. For the simultaneous evacuation of damaged hospitals, a fleet of two hundred converted busses carrying 10 stretcher cases and 6 to 10 sitting cases are immediately available and another two hundred are obtainable within two hours.

4. Casualty stations (British fixed first aid posts) are necessary at or near all hospitals and at places more than a mile from hospitals to care for minor casualties which do not require hospitalization. Many are now on a care and maintenance basis and are activated only during a raid. When functioning, the staff usually consists of one or two doctors, several nurses and a variable number of aides and auxiliaries.

5. In large cities casualty stations need not be more numerous than one to 25,000 inhabitants; they should be located about a mile apart. There are less than three hundred in the London area with a population of about 10,000,000 and a land area more than twice that of greater New York. In smaller, thinly settled communities, they are more numerous in relation to population but the distances between them are proportionately greater than in metropolitan cities. Many of the minor casualties are moved to first aid posts in sitting case cars; some walk.

6. First aid parties (our stretcher teams) are not necessary, are a waste of manpower and are rapidly being eliminated. First aid at incidents is essentially a function of the rescue parties (our rescue teams), which extricate the casualties from under the débris of demolished buildings. All first aid parties in England and Scotland are therefore being merged into the rescue parties. They include a leader, an assistant leader and eight other members and are entirely independent of the fire department. They are a life saving service related to the medical services concerned in field casualty work.

7. The experiences of Britain under air raid conditions have dispelled many preconceived notions concerning first aid. Almost all raids occur at night; the victims are crushed under the débris of demolished buildings and are either dead or severely injured; less than a third are slightly injured and can be cared for at casualty stations; all the severely injured must go directly to a hospital; victims are invariably covered with dust and dirt, which hangs in the air for hours. The conditions under which the rescue workers encounter the injured beneath the structural débris, the darkness and the dust which always fills the air, the large proportion of dead and severely injured, and the urgent need for immediate hospitalization make it impossible to apply most peacetime concepts of first aid.

8. Wounds are usually grossly contaminated and need only be covered with a shell dressing until the casualty reaches the hospital. Hemorrhage is usually controllable with a pressure dressing. The tourniquet is rarely employed. Burns are covered only with sterile gauze until the casualty arrives at the hospital. Tannic acid jelly as a first aid dressing for burns has been discarded because of the dirt which invariably contaminates the burned surface, because the jelly deteriorates rapidly and, lastly, because tannic acid ignites in the presence of phosphorus when applied to burns caused by the explosion of phosphorus-oil bombs.

9. Traction splints are not used. An exception is made if the casualty must be transported a long distance over country roads. Unlike army field experience in the last war, the few miles of travel to a hospital over the paved roads of a city do not warrant the application of traction, especially as the darkness and the conditions of an air raid also make hurried application of the procedure difficult or impossible. All that can be done is to place the fractured extremity gently in alinement, bind it with triangle bandages to the uninjured leg or to an improvised splint, or apply a Thomas splint if one is at hand. Movement of the fragments can also be minimized by snug application of the blankets according to the Wanstead technic of blanketing and by the use of sand bags, which should always be carried in the ambulance.

10. Shock is treated at the incident by prompt administration of adequate doses of morphine (up to ½ grain for adults), nikethamide, proper blanketing, administration of fluids and the use of hot water bottles during transportation to the hospital. The use of plasma or blood transfusion is deferred until arrival at the hospital; it is ordinarily quite impossible in the darkness, dirt and confusion at the incident.

11. The presence of a physician at the incident is invaluable but more than one is unnecessary. In fact, one physician may cover several nearby incidents, leaving his nurse or one of the nursing auxiliaries of his emergency team at the incident while he moves temporarily from one to another in the immediate neighborhood.

12. Even though a single night's casualties requiring hospitalization may total 1 or 2 thousand, large hospitals rarely receive more than 50 to 100, the load being distributed as evenly as possible throughout the city.

13. A large casualty receiving hospital is often related to one or more peripheral hospitals in the suburbs or in a country district. There are now four base hospital beds for each casualty bed in the cities.

14. On receipt at a local report and control center of a message from an air raid warden that an incident and casualties have occurred, an "express party" is immediately dispatched to the scene. An "express party" includes one rescue first aid party, one ambulance, one sitting case car and one mobile medical unit (our mobile medical team). The latter consists of one physician, one nurse and two auxiliaries. No other equipment and personnel of the emergency medical service is dispatched unless additional assistance is requested by the incident officer (usually a higher police official) or by the incident physician on the scene. In this manner useless movement is avoided and equipment and personnel of the community are carefully conserved.

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ORGANIZATION SECTION

OFFICIAL NOTES

ARMY AND NAVY PHYSICIANS LISTED IN THE DIRECTORY AT WASHINGTON

For military reasons, medical officers of the regular U. S. Army and the U. S. Navy, on active duty, were listed in the new Seventeenth Edition of the American Medical Directory at Washington, D. C., with biographic data, titles, and local addresses as U. S. Army and U. S. Navy.

Officers of the Medical Reserve Corps, the Naval Reserve and the National Guard who are on extended active duty are listed at their home addresses followed by a symbol indicating their respective branch of service.

Reserve officers for whom home addresses could not be obtained are also listed at Washington, D. C., without local addresses.

Users of the American Medical Directory are requested not to send mail to officers listed at Washington, D. C., when only the address of the U. S. Army or the U. S. Navy is shown.

DOCTORS AT WAR

Owing to schedule conflicts, Doctors at War, which goes on the National Broadcasting Company network Saturdays at 5 p. m. eastern time, beginning December 26, cannot be broadcast in Chicago at that time. The program, therefore, will be heard in Chicago on a rebroadcast from 8 to 8:30 p. m. central time, over station WMAQ. Similar program conflicts may materialize in other communities. If the program is not heard at the regular time, local newspaper radio announcements should be consulted.

Persons who are interested in assuring local broadcasts of the program might profitably call the action of WMAQ in this regard to the attention of their local radio program department. It should be noted that the Blue Network, which is no longer the property of the National Broadcasting Company, cannot procure Doctors at War.

MEDICAL LEGISLATION

MEDICAL BILLS IN CONGRESS

Changes in Status.—H. R. 7633 has passed the House, providing for an increase in pay and allowances for members of the Army Nurse Corps and providing for the inclusion in the Medical Department of the Army of such female dietetic and physical therapy personnel as the Secretary of War may consider necessary. As passed by the House, this bill provides that the superintendent of the Army Nurse Corps will have the relative rank of colonel, assistant superintendents or directors will have the relative rank of lieutenant colonel or major respectively, the director of dietitians and the director of physical therapy aides will each have the relative rank of major, and all other assistant superintendents and assistant directors, chief dietitians and chief physical therapy aides will have the relative rank of captain. Chief nurses, head dietitians and head physical therapy aides will have the relative rank of first lieutenant, and head nurses, nurses, dietitians and physical therapy aides will have the relative rank of second lieutenant. Employment by the military establishment of female dietetic and female physical therapy personnel will hereafter be limited to persons appointed under the provisions of this bill, and appointments of such personnel under the provisions of any other law will be terminated as of the last day of the third month following the month in which the bill is enacted. The provisions of this bill relating to the Army Nurse Corps and to female dietetic and female physical therapy personnel will remain in effect during the present war and until six months thereafter. S. 2769 has been reported to the Senate, authorizing the rank of rear admiral in the Dental Corps of the United States Navy.

WOMAN'S AUXILIARY

Iowa

Members of the Polk County auxiliary have served as hostesses at the USO in Des Moines on the first and the third Wednesday of each month. Ten members furnish the refreshments and four serve them.

Oklahoma

As early as 1917 there was an auxiliary organized in Shawnee, and Oklahoma has had a state organization since 1928. At present there are ten counties organized in the state, with a total membership of 360. One of the primary goals for the state auxiliary this year is to form auxiliaries in the unorganized counties.

The Cleveland County auxiliary has sponsored a Red Cross course in home nursing, which has been taught by one of their members. The entire auxiliary is active in Red Cross work.

Wisconsin

The woman's auxiliary to the Washington-Ozaukee County Medical Society met on September 10 at the Ozaukee Country Club. Guests included Mrs. Robert Radtke, Watertown; Mrs. J. Eichman, Allenton; Mrs. W. T. Becker and Mrs. V. A. Waldren, Cedarburg, and Miss Elizabeth Carthaus, Thiensville. News from the twentieth anniversary meeting of the national auxiliary at Atlantic City in June, as reported in the *Bulletin*, was reviewed by Mrs. A. H. Barr, Port Washington. The October meeting of the auxiliary was held in Port Washington. Following a 1 o'clock luncheon, the business meeting was held at the home of Mrs. C. C. Stein.

The auxiliary to the Waukesha County Medical Society met at the home of its president, Mrs. T. H. Nammacher, Oconomowoc, on October 7. Members heard the annual reports of the committee chairmen and were particularly interested in the scrapbook compiled by Mrs. W. T. Murphy, Waukesha, archives chairman.

Dr. P. E. Pifer, president of the Kenosha County Medical Society, spoke to the woman's auxiliary on "Excerpts of Legendary Medicine" at the home of Mrs. C. F. Ulrich on October 6. At the business meeting, the members decided to work on surgical dressings for the Red Cross each Thursday afternoon. Mrs. Alexander Schlapik announced that the group would send meat or fowl to the canteen each month.

The Womans Auxiliary to the Medical Society of Milwaukee County met on October 9 at the Pfister Hotel. Forty members greeted the incoming president, Mrs. H. O. Zurheide. The Reverend Lee J. Ferry spoke on "Associated Charities" and Mr. Richard Rice discussed "Civilian Defense." Members enjoyed violin solos by Mrs. Benjamin Lieberman and dramatic readings by Miss Inez Shabart. At a board meeting approval was voted to further the educational campaign of the Women's Field Army for the Control of Cancer.

Medical News

(Physicians will confer a favor by sending for this department items of news of more or less general interest: such as relate to society activities, new hospitals, education and public health.)

CALIFORNIA

Faculty Changes at Stanford.—Dr. Harold Phillips Hill, clinical professor of medicine, San Francisco, Stanford University School of Medicine, San Francisco, has been made professor emeritus. Full professorships have been granted to Dr. Victor E. Hall in physiology; John Field II, Ph.D., in physiology, and Dr. Charles E. Smith in public health and preventive medicine.

Society News.—The San Francisco County Medical Society devoted its meeting October 13 to a consideration of practical aspects of the problems of resuscitation. The speakers were Drs. Hubert R. Hathaway, William B. Neff, John A. Stiles and Leon Goldman, all of San Francisco. —— Dr. Paul C. Bucy, Chicago, discussed "Motor Cortex and Its Relation to Athetosis and Tremor" before the Hollywood Academy of Medicine October 8.

Dr. Addis Awarded Cullen Prize.—Dr. Thomas Addis, since 1919 professor of medicine at Stanford University School of Medicine, San Francisco, has been awarded the Cullen Prize by the Royal College of Physicians in Edinburgh for "the greatest benefit done to practical medicine in the last four years." Dr. Addis, whose research has included extensive study on the kidney, is a native of Edinburgh and a member of the Royal College of Physicians.

Grants for Tropical Disease Studies.—The Josiah Macy Jr. Foundation, New York, recently gave $4,000 to Stanford University to aid studies in tropical diseases. Other recent grants for the same research include $850 from the Carnegie Corporation of New York; $400 from the National Academy of Sciences and $200 from the May Esther Bedford Fund, Inc., of Connecticut. Other subscribers to this cooperative project at Stanford are the Higher Studies Fund at Oxford, the British Association for the Advancement of Science, the Ella Sachs Plotz Foundation for the Advancement of Scientific Investigation, New York, and the Viking Fund, Inc., New York. Edward P. Mumford, M.Sc., research associate, biology, is directing the project, which is an investigation of the geographic distribution of insects and other disease carriers and of the parasites of man in relation to the war and its aftermath. According to an announcement from Stanford University, the study is being made with special emphasis on the Pacific Islands, with which Mr. Mumford has been concerned in his research at Stanford since 1939.

COLORADO

State Medical Election. — Dr. George P. Lingenfelter, Denver, was recently chosen president-elect of the Colorado State Medical Society and Dr. Ralph S. Johnston, La Junta, was inducted into the presidency. Dr. Edward R. Mugrage, Denver, was named vice president and Dr. John S. Bouslog, Denver, was reelected constitutional secretary. Mr. Harvey T. Sethman, Denver, is the executive secretary.

New Editor of State Journal.—Dr. Lyman W. Mason, Denver, assistant professor of obstetrics and gynecology, University of Colorado School of Medicine, has recently been made acting scientific editor of the *Rocky Mountain Medical Journal*. Dr. Douglas W. Macomber, Denver, was granted a leave of absence from the position to become a major in the medical corps of the Army of the United States.

ILLINOIS

Society News.—Dr. Herbert E. Landes, Chicago, discussed hematuria before the McLean County Medical Society at Bloomington, November 17.——Dr. Alfred D. Biggs, Chicago, addressed the Kankakee County Medical Society, November 10, on problems of the newborn.

Chicago

Dr. Landau Named Director of X-Ray Department.—Dr. George M. Landau, director of the x-ray department of the Cook County Infirmary, Oak Forest, Ill., has been appointed director of the x-ray department of Cook County Hospital, filling the vacancy caused by the death of Dr. Maximilian Hubeny last July. Dr. Landau graduated at the University of Illinois College of Medicine in 1915.

The William T. Belfield Lecture.—Dr. Andrew C. Ivy, recently appointed chief scientific director of the U. S. Naval Medical Research Institute, Bethesda, Md., and Nathan Smith Davis professor of physiology and pharmacology, Northwestern University Medical School, gave the fourteenth annual William T. Belfield Memorial Lecture before the Chicago Urological Society, November 19, on "The Physiology of the Urinary Bladder, with Special Reference to Its Nerve Supply."

University Blood Bank.—A blood and plasma bank for the treatment of civilian patients is now in operation at the University of Illinois College of Medicine to serve the Research and Educational Hospitals and allied institutes in Chicago. Dr. Milan V. Novak, associate professor of bacteriology and public health at the medical school, is in charge of the blood and plasma library. The project is not connected with the blood bank program of the American Red Cross but is intended to help the hospitals, it was stated.

Fellowships in Industrial Surgery. — Dr. William A. Larmon and John W. Henderson have been awarded the first two of the James S. Kemper fellowships in industrial surgery at Northwestern University. The amount of $5,000 was awarded by Mr. James S. Kemper to subsidize fellows at the medical school to be trained in general surgery with special emphasis on industrial phases. The recipients will receive their training in the various hospitals affiliated with the university and the dispensary and the laboratories in the Montgomery Ward Building.

Drs. Hektoen and Herrick Honored.—Dr. Ludvig Hektoen and Dr. James B. Herrick will be honored at the twenty-seventh annual dinner of the Institute of Medicine of Chicago in the Grand Ballroom of the Palmer House on December 2, in recognition of their many years of service to the institute. Dr. Wilber E. Post will preside at the dinner and speakers will be Dr. James P. Simonds, professor of pathology at Northwestern University Medical School, on "Ludvig Hektoen: A Study in Changing Scientific Interests" and Mr. J. Christian Bay, librarian, John Crerar Library, "James B. Herrick: Youth in Man Makes History." Dr. Hektoen and Dr. Herrick are two of the founders of the Institute of Medicine and have been active on the board of governors since 1915, when the institute was founded. Dr. Herrick was president in 1925 and Dr. Hektoen in 1929. Dr. Hektoen was also chairman of the board of governors from 1921 to 1940, when he became honorary chairman.

The De Lee Memorial Fund. — More than $50,000 to establish the Joseph B. De Lee Memorial Fund was presented to the University of Chicago November 23 at a meeting honoring the late Dr. De Lee, founder of the Chicago Lying-in Hospital. The fund will be used to provide fellowships in the Chicago Lying-in Hospital for young physicians engaged in the specialized study of obstetrics. Dr. Morris Fishbein, Editor of The Journal, and Robert M. Hutchins, LL.D., president of the University of Chicago, were the principal speakers at the meeting. Dr. Fishbein's subject was "Maternal Care in the Post-War Period." The presentation of the fund was made by Dr. M. Edward Davis, professor of obstetrics and gynecology at the university's school of medicine and obstetrician and gynecologist at the hospital. Ultimately the fund will be increased to $100,000. The largest single contribution of $20,000 was a gift from the Mothers' Aid of the hospital. The present hospital is the outgrowth of a one man dispensary started by Dr. De Lee. In 1917 it was housed in its first modern building. The present building was completed in 1931, and in 1938 the hospital was merged with the University Clinics. Dr. De Lee was head of the hospital from its beginning until his retirement in 1939. He died April 2 of this year.

KENTUCKY

Society News.—The Jefferson County Medical Society was addressed November 16 by Drs. Wilfrid C. Gettelfinger on "Cirrhosis of the Liver" and Charles H. Maguire, "Pyloric Stenosis." Drs. William Austin Bloch and Maurice G. Buckles presented a case report on "Carcinoma of the Lung." All are of Louisville.——Dr. William Barnett Owen, Louisville, discussed the Kenny treatment of poliomyelitis before the Louisville Medico-Chirurgical Society November 13.

Industrial Health Program.—As a result of a meeting in Louisville, October 9, fifty new committees have been appointed to organize subcommittees on industrial health and welfare in the state. More than a hundred representatives of labor and management attended the meeting, at which the medical, engineering, safety and welfare offices of a good industrial hygiene program were discussed by prominent industrial hygiene and

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safety experts. Reporting of occupational diseases is now required by law in Kentucky, thirty-four of which are included in a list of diseases "declared dangerous to the public health." The list is being sent to all physicians in the state.

MARYLAND

Society News.—The Baltimore City Medical Society was addressed November 6 by Drs. Philip B. Price on "Zinc Iontophoresis in Treatment of Carbuncles"; Edward M. Hanrahan Jr., "The Treatment of Advanced Carcinoma of the Scalp and Skull," and Leo Brady, "The Treatment of Leukorrhea Due to Trichomonas Vaginalis"; all are from Baltimore.

MASSACHUSETTS

Worcester Medical Library Moves.—The Worcester Medical Library of the Worcester District Medical Society has been moved from its headquarters at 34 Elm Street to 57 Cedar Street, Worcester. The new quarters will also serve as a home for the society and accommodate the society's blood bank (THE JOURNAL, September 26, p. 299).

Activities at Harvard.—Dr. Joseph S. Lichty, Shaker Heights, Ohio, of the Cleveland Trust Company has been been appointed assistant dean of the faculty of medicine at Harvard University and assistant professor of medical administration. Dr. Franklin F. Snyder, Chicago, has been appointed associate professor of anatomy and obstetrics at the medical school. Frederick J. Stare, Ph.D., Madison, Wis., has been appointed assistant professor of nutrition, which is reported to be a new title connecting the clinical and laboratory branches of nutritional science. Dr. Stare will work both in the laboratory and in the field in connection with the medical school and the school of public health. Henry P. Treffers, Ph.D., an immunochemist, has been named to a new title at Harvard, that of assistant professor of comparative pathology and biologic chemistry. A new office, known as "Medical School Research Laboratories," has been organized in the medical school under Mr. U. Haskell Crocker. The object is to coordinate and centralize the business details of the various research projects in progress in the medical school, operating under contract with the office of scientific research and development.

MISSISSIPPI

Changes in Health Personnel.—Dr. William D. May, Meridian, has been named director of the Alcorn County Health Department, succeeding Dr. Robert H. DeJarnette, Corinth, who has entered the army.——Dr. John H. Hines, Canton, has resigned as health officer of Madison County to join the army. ——Dr. James F. Bradley, Liberty, has been appointed health officer of Noxubee County, succeeding Dr. George E. Gibbons, Macon.——Dr. Margaret M. Scannell, formerly of Meridian, has been named medical director of the Sunflower County Department of Health, succeeding Dr. Andrew Hedmeg, Indianola, who has entered the military service.——Dr. Thomas Burk, Rayville, La., has been appointed health officer of Copiah County with offices in Hazlehurst, succeeding Dr. John C. McGuire, Hazlehurst.

MISSOURI

New Professor of Psychiatry.—Dr. Edwin F. Gildea, formerly associate professor of psychiatry at Yale University School of Medicine, New Haven, Conn., is now professor of psychiatry and administrative head of the department of neuropsychiatry at Washington University School of Medicine, St. Louis. Dr. Gildea graduated at Harvard Medical School, Boston, in 1924.

First Terry Lecture.—The first annual Robert J. Terry Lecture will be delivered before the St. Louis Medical Society, December 1, by Dr. Stuart Mudd, Philadelphia, on "Morphology of Pathogenic Bacteria and Viruses as Shown by the Electron Microscope, with Some Practical Implications." The lecture was established through a bequest in the will of the late Dr. William T. Coughlin, a former member of the society. The will stipulated that the income from a bequest of $5,000 be used to establish and maintain a lecture or lectures to be given annually at the Medical Society Building and to be known as the "Robert James Terry Lecture (or Lectures)." Dr. Coughlin stated in his will: "This I do as a testimonial of my gratitude to Dr. Terry, who gave me a position as assistant in his laboratory, which afforded me not only an opportunity to learn the anatomy of the human body and thus to fit myself for surgery but also the means whereby I was enabled to begin my practice in St. Louis." Dr. Coughlin died on May 22, 1940. Dr. Terry is professor emeritus of anatomy at Washington University School of Medicine.

NEW JERSEY

Explosion of Anesthetic Kills Patient.—According to the New York *Times* an explosion of an anesthetic killed a patient, November 10, as he was receiving a blood transfusion after a chest operation at the New Jersey Sanatorium for Tuberculous Diseases at Glen Gardner. Internal hemorrhage caused the death of the 25 year old patient fifty minutes after the explosion. Physicians and others working in the operating room were not injured. William J. Ellis, Ph.D., Trenton, state commissioner of institutions and agencies, said a static spark was the only plausible explanation of the explosion, and the mishap was "beyond human power to anticipate." The room was adequately protected against a spark from any of the electrical apparatus. It was explained that the explosion occurred as the mask hose was being removed from the machine which mixed cyclopropane gas with oxygen. There was no negligence on the part of any one, it was stated. It was further reported that the patient was in an advanced stage of tuberculosis and the chest operation was decided on as the only means of saving his life.

NEW YORK

Mr. Armstrong Dies.—Charles Ralph Armstrong, for thirty years superintendent of the Trudeau Sanatorium, Trudeau, died, November 9, aged 71.

Society News.—The Onondaga County Medical Society and the Syracuse Academy of Medicine were addressed, November 10, by Drs. Percival K. Menzies on "Traumatic Rupture of the Liver" and Robert K. Brewer, "Review of Liver Function Tests."——Dr. Walter Brandon Macomber, Albany, discussed "Principles of Plastic Surgery and Their Application" before the Medical Society of the County of Albany, November 25.

New York City

New Women's Field Army Headquarters.—The board of managers of the Memorial Hospital for the Treatment of Cancer and Allied Diseases has given the Women's Field Army of the New York City Cancer Committee space in its old building at Central Park West and 106th Street for new headquarters and the workroom of the surgical dressings committee. Space has also been given in the same building for a permanent exhibit of the cancer educational material of the city cancer committee.

Portrait of Dr. Walter Niles.—A portrait of the late Dr. Walter L. Niles was presented to Cornell University Medical College, November 13. Joseph C. Hinsey, Ph.D., dean, presided at the presentation ceremonies. Dr. Malcolm Goodridge, president of the New York Academy of Medicine, gave the memorial address. Dr. Connie M. Guion, chairman of the portrait committee, made the presentation, and Edmund E. Day, LL.D., president of the school, gave the speech of acceptance. Dr. Niles graduated at Cornell in 1902. He was professor of clinical medicine from 1916 until his death in 1941 and had been dean from 1919 to 1928. He was acting dean of the school at the time of his death.

Refresher Course in Cardiovascular Diseases.—The New York Academy of Medicine and the New York Heart Association are cooperating in a series of lectures on cardiovascular diseases. The first in the series was delivered on November 25 by Dr. Robert L. Levy on "Management of the Patient Who Has Recovered from Acute Coronary Occlusion." Others in the series will be:

Dr. William Goldring, December 23, The Management of Hypertension.
Dr. Edwin P. Maynard Jr., Brooklyn, January 27, The Management of Cardiovascular Syphilis.
Dr. Harry Gold, February 24, The Management of Heart Failure.
Dr. Irving S. Wright, March 24, The Management of Peripheral Vascular Disease.
Dr. Currier McEwen, April 28, The Management of Rheumatic Fever.
Dr. Arthur C. De Graff, May 26, The Management of Cardiac Arrhythmias.

Agencies Merge to Care for Orphans.—The Home for Hebrew Infants and the New York Association for Jewish Children, child care agency of the Federation for the Support of Jewish Philanthropic Societies of New York City, have been merged, completing the integration into one body of all federation agencies devoted to the care of orphaned and dependent children, including institutional care, foster home care and aftercare for graduates of institutions and foster homes. The merged group will bear the name of the New York Association for Jewish Children and under the consolidation becomes the largest single child care agency in the country, according to the New York *Times*. Infants now in the home at 100 West Kingsbridge Road are being placed in foster homes under the supervision of the association, and the building will serve as administrative center for the boarding out of children.

Radiologic Laboratory Established.—The establishment of a radiologic research laboratory as part of the cancer research program at Columbia University was announced on November 12. The effect of radiation on living cells will be the main concern of the new laboratory and, in connection with this, the Florence Nightingale Hospital for cancer patients will be built by the city at One Hundred and Sixty-Third Street and Fort Washington Avenue, near the Medical Center. Special attention will be given to treatment in which high voltage x-rays are used to destroy cancer, it was stated. A million volt therapy machine will be installed in Presbyterian Hospital and Sloane Hospital for Women in connection with the plan but priorities have delayed installation. Gioacchino Failla, Sc.D., physicist at Memorial Hospital for the Treatment of Cancer and Allied Diseases, will direct the laboratory. His assistants will be Edith H. Quimby, A.M., associate physicist at Memorial Hospital, and Titus C. Evans, Ph.D., research associate professor of radiology at the State University of Iowa College of Medicine, Iowa City.

Dr. Crumbine Honored.—Dr. Samuel J. Crumbine, for many years prominently active in the field of public health, was guest of honor at a dinner at the Waldorf-Astoria, November 12, given by the Kansas Society of New York. Dr. Crumbine observed his eightieth birthday this year. Born in Emlenton, Pa., in 1862, Dr. Crumbine graduated at the Cincinnati College of Medicine and Surgery in 1889. He was a member of the Kansas State Board of Health from 1898 to 1904 and secretary from then until 1923. He was dean of the University of Kansas School of Medicine from 1911 to 1919. In 1914 he was president of the State and Provincial Health Authorities of North America. He joined the American Child Health Association in 1923 as director of states relations. From 1925 until the association was disbanded in 1935, Dr. Crumbine served as general executive. The speakers at the recent dinner included Charles P. Taft, LL.D., assistant federal director, Defense, Health and Welfare Services, Washington, D. C.; Hon. Payne H. Ratner, Topeka, Kans., governor of Kansas; Osa H. Johnson; H. Clyde Holmes, president of the Kansas Society of New York; Lloyd Stratton, assistant general manager of the Associated Press; Hon. Henry J. Allen, Witchita, Kans., former governor of Kansas, who served as toastmaster, and Dr. Crumbine.

OREGON

Deaths at State Hospital Attributed to Poison.—Forty-seven deaths occurred at the Oregon State Hospital, Salem, and more than 450 inmates became ill after a meal in which scrambled eggs were served, November 18. Newspaper reports indicate that a patient who had been given storeroom keys "in violation of institution rules entered the wrong storeroom when sent for powdered milk and brought back six pounds of roach powder." The roach powder resembles powdered milk and the assistant cook admitted, it was stated, that he mixed it with the eggs without noticing the error. George A. Posen, an epileptic patient, admitted that he measured out roach powder by mistake when sent to the storeroom by the assistant cook. Credit was given to Mrs. Allie Wassel, aged 63, a kitchen attendant, for saving many lives by ordering all patients to quit eating after she herself had tasted the eggs and became violently ill. The institution has 2,800 patients, about 1,400 of them men.

PENNSYLVANIA

Portrait of Dr. Pfahler.—A portrait of Dr. George E. Pfahler, professor of radiology at the University of Pennsylvania School of Medicine, Philadelphia, and since 1935 a member of the board of directors of Ursinus College, Collegeville, was unveiled during special services held to name the Hall of Science at Ursinus College in honor of Dr. Pfahler. The portrait was presented to the college by Mrs. Pfahler and is the work of Mr. Robert Susan. It now hangs in the foyer of the science building (THE JOURNAL, November 14, p. 853).

Philadelphia

The Packard Memorial Lecture.—Dr. Martha M. Eliot, associate chief, Children's Bureau, U. S. Department of Labor, gave the Frederick A. Packard Memorial Lecture before the Philadelphia Pediatric Society, November 10. Her subject was "Children in Wartime."

Medical Club Celebrates Fiftieth Anniversary.—The Medical Club of Philadelphia held a dinner meeting at the Union League, October 16, to observe the fiftieth anniversary of its founding. Dr. Walt P. Conaway, Atlantic City, N. J., presided and acted as toastmaster. Mr. C. William Duncan, a Washington correspondent and formerly associated with the now defunct *Evening Public Ledger* of Philadelphia, was the guest speaker. Three hundred and twelve members and guests attended the dinner meeting, at which nominees were chosen for the elections to be held in January.

Dr. Lewis Retires as Medical Director.—Dr. Mary R. H. Lewis was guest of honor at a dinner, November 4, given by the staff of the Woman's Hospital to mark her retirement as medical director of the hospital. Dr. Lewis, who graduated at the Woman's Medical College of Pennsylvania in 1911, served her internship at the Woman's Hospital, Philadelphia, and has been connected with that hospital ever since as associate in obstetrics and later as chief of the department. For eleven years she was physician to women and lecturer in hygiene at Swarthmore College and in private practice in Swarthmore. Dr. Lewis was medical director of the West Philadelphia Hospital for Women from 1918 until it merged with the Woman's Hospital in 1929, when she became medical director of the new Woman's Hospital. Dr. Dorothy Donnelly-Wood was toastmistress at the dinner.

Tuberculosis Conference.—A symposium on x-ray survey at the United States Navy Yard opened the annual Philadelphia Tuberculosis Conference, November 10, at the Ritz-Carlton Hotel. The speakers were Dr. William Edward Chamberlain; Dr. David A. Cooper; Captain Earl C. Carr, senior medical officer, U. S. Navy; Dr. Horace R. Getz, and Commander Edward L. Bortz, M. C., U. S. Naval Reserve. Dr. George Morris Piersol presided. At the luncheon session presided over by Dr. Charles J. Hatfield, president of the Philadelphia Tuberculosis and Health Association, Dr. Hubley R. Owen, city director of health, discussed "Tuberculosis and Other Health Problems in England." The theme of the afternoon session, with Dr. William Harvey Perkins presiding, was "Tuberculosis and War," with the following speakers: Major General Charles R. Reynolds, M. C., U. S. Army, retired; Lieutenant Colonel Esmond R. Long, office of the Surgeon General, U. S. Army; Herman E. Hilleboe, passed assistant surgeon, U. S. Public Health Service; Dr. Abraham J. Cohen, and Dr. Hubert W. Hetherington.

Pittsburgh

Meeting of Psychiatrists.—The fourth annual dinner meeting of the Pennsylvania Psychiatric Society was held at the University Club on October 8. Col. Leonard G. Rowntree, M. C., A. U. S., Washington, D. C., chief, medical division, Selective Service System, spoke on "Selective Service and Psychiatry." An afternoon session at the Western State Psychiatric Hospital was addressed by Dr. William C. Sandy, Harrisburg, on "The State Bureau of Mental Health and the Problems Presented by the War"; Dr. Grosvenor B. Pearson, "The Western State Psychiatric Hospital," and Dr. Herbert H. Herskovitz, Norristown, "Psychiatric Aspects of Service Men Transferred to the Norristown State Hospital."

TEXAS

Lectures on Mental Hygiene.—The Hogg Foundation of the University of Texas, Austin, under the direction of Robert L. Sutherland, Ph.D., professor of sociology, has arranged a series of special lectures on mental hygiene at the University of Texas Medical Branch, Galveston, and at other medical centers through the state. Dr. Tom Alfred Williams, London, discussed war problems relating to traumatic neuroses and shell shock. A symposium was conducted during November by Drs. Emilio Mira, professor of psychiatry, University of Buenos Aires, Argentina, C. Charles Burlingame, Hartford, Conn., and Lieut. Col. Franklin G. Ebaugh, M. C., U. S. Army. In January Dr. Walter L. Treadway, medical director, U. S. Public Health Service, formerly chief of the division of mental hygiene of the service, will survey mass problems of mental hygiene during the war.

New Appointments in Cancer Project.—The M. D. Anderson Foundation, Houston, which is financing with the state the development of the Texas State Cancer Hospital and Research Laboratories, has added to the staff of the new new project J. K. Kline, Ph.D., and Fritz Schlenk, Ph.D., associate and assistant professor, respectively, of preventive medicine and public health at the University of Texas Medical Branch, Galveston. Dr. Kline worked with Robert Williams, D.Sc., on the synthesis of thiamine (vitamin B_1) and has recently been engaged in cancer research in Galveston. Dr. Schlenk was engaged in enzyme research in Stockholm before the war and has since been conducting nutritional studies relating to disease at Galveston. Collaboration is being arranged between the new cancer hospital in Houston and the institute of biochemistry at the University of Texas, Austin. A tumor clinic has been established at the John Sealy Hospital of the University of Texas, Galveston, to cooperate with the Houston institution.

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WISCONSIN

Third Annual Dearholt Day.—The third annual "Dearholt Day" was observed in Madison, November 17, under the auspices of the Wisconsin Anti-Tuberculosis Association, the University of Wisconsin Medical School and the Dane County Medical Society. Drs. Florence R. Sabin, Denver, formerly a member of the Rockefeller Institute for Medical Research, and David T. Smith, professor of bacteriology and associate professor of medicine, Duke University School of Medicine, Durham, N. C., were the speakers. Dr. Sabin discussed "The Functions of the Reticulo-Endothelial Cells" and "Cellular Reactions in Antibody Formation" and Dr. Smith gave two talks on "Diagnosis and Treatment of Certain Nontuberculous Infections of the Lungs Which Simulate Tuberculosis." The special observance is held in honor of the late Dr. Hoyt E. Dearholt, Milwaukee, for many years executive secretary of the Wisconsin Anti-Tuberculosis Association. A similar program was held in Milwaukee November 16 in cooperation with Marquette University School of Medicine, Muirdale Sanatorium, the Milwaukee Academy of Medicine and the tuberculosis division of the Milwaukee health department.

GENERAL

New Editor in Chief for Pathology Journal.—Dr. Israel Davidsohn, Chicago, has been named editor-in-chief of the *American Journal of Clinical Pathology*, succeeding Dr. Robert A. Kilduffe, Atlantic City, N. J., who has entered military service.

Survey of Plantations in Search for Cinchona Bark.—As a part of the effort to conserve quinine, Norman Taylor, director of Cinchona Products Institute, Inc., New York, is leaving soon for tropical America for a survey of plantations and sources of cinchona bark. The trip, which will include the region from southern Mexico to Bolivia, has been authorized by the board of commissioners for the Netherland East Indies, and its purpose is a cooperative one in the war effort with governmental agencies and manufacturers so that adequate supplies of cinchona bark may be available.

New Tuberculosis Officers.—Dr. Victor F. Cullen, State Sanatorium, Md., was elected president of the Southern Tuberculosis Conference at the annual meeting in Memphis, October 5-7. Logan H. McLean, Sanatorium, Miss., was chosen vice president and J. P. Kranz, Nashville, Tenn., secretary-treasurer. ——Dr. Horton R. Casparis, Nashville (deceased), was elected president of the Southern Trudeau Society at its meeting in Memphis, Tenn., October 5-7. Other officers of the group are Drs. Duane M. Carr, Memphis, vice president and Julius L. Wilson, New Orleans, secretary-treasurer.

Annual Christmas Seal Sale.—The thirty-sixth annual Christmas Seal Sale of the National Tuberculosis Association and its 1,700 affiliated associations throughout the country opened November 22. Eight million dollars has been set as the national total of the sale. Ninety-five per cent of the seal sale income remains in the state in which it is raised and 5 per cent of each state's return goes to support the work of the national association. As in all past wars, tuberculosis is on the increase, Dr. Kendall Emerson, managing director of the national association, stated in a release to the press. It has risen alarmingly in Europe and Asia, he said, but so far in this country preliminary figures for 1942 indicate that tuberculosis deaths will be the lowest on record. He also stated that the full impact of the war on the campaign to control tuberculosis will probably be felt during the coming year. Dr. Emerson, in outlining the major activities of the tuberculosis association for the coming year, stressed medical research, the expansion of x-ray surveys among industrial workers, particularly young women, full assistance to men rejected from the armed forces because of tuberculosis, cooperation in the health program of the High School Victory Corps, and a health education campaign to emphasize the need and ways of maintaining a high resistance to the disease.

Society News.—Mr. Frank J. Walter, Denver, was chosen president-elect of the American Hospital Association at its recent annual meeting in St. Louis. Mr. James A. Hamilton, New Haven, was installed as president, Dr. Harley A. Haynes, Ann Arbor, is the treasurer and Dr. Bert W. Caldwell, Chicago, is the executive secretary. The 1943 session will be held in Buffalo.——The American Medical Women's Association will hold its annual midyear board meeting in Cincinnati, December 5-6. Mrs. Oveta Culp Hobby, director of the Woman's Army Auxiliary Corps, will be the principal speaker at the banquet at the Netherland Plaza Hotel, December 5.—— Dr. John Walker Moore, Louisville, Ky., was elected president of the Central Society for Clinical Research at its annual meeting in Chicago November 6-7, Dr. Cecil J. Watson, Minneapolis, vice president and Dr. Carl V. Moore, St. Louis, secretary-treasurer.

Million Dollars Pledged for Diet Research.—A fund of $1,001,000, pledged to the Nutrition Foundation, Inc., to support a five year program of basic research in the science of nutrition, has been contributed by a group of food and related manufacturers. The announcement was made at a meeting of the foundation at the Chicago Club, Chicago, November 12. Eighteen additional grants-in-aid totaling $46,000 were appropriated by the foundation's board of trustees making a total of fifty-four grants allocated this year to thirty-three universities, colleges and medical centers. Among the universities receiving new grants are Northwestern, Chicago; Illinois, Urbana-Champaign; Notre Dame, South Bend, Ind., and Wisconsin, Madison. Previous grants had been awarded to the Universities of Chicago, Illinois, Minnesota, Purdue, Wayne, Wisconsin, Northwestern and the Children's Fund of Michigan, Detroit. Other institutions receiving grants at the foundation's meeting in Chicago include the Universities of Virginia, Arkansas, Stanford, Rochester, Southern California, Cornell and California, and the Alabama Polytechnic Institute, Auburn; Harvard Medical School, Boston; Mount Sinai Hospital, New York Postgraduate Medical School and Hospital, and the Memorial Hospital for the Treatment of Cancer and Allied Diseases. The new type of studies now being supported by the foundation include isolation of unstable food factors, protein utilization during partial starvation, utilization and distribution of radioactive iron, protection of the teeth afforded by specific nutrients, liver synthesis of blood proteins, nutritive protection against infection, the relation of vitamin A to muscle metabolism, nutritive value of low cost vegetables, minimum vitamin needs of adults, metabolic balances in diabetes, nutritive protection of the blood vessels and the nutrient in cow's milk under specific conditions. It was announced also that the Safeway Stores, Inc., Oakland, Calif., and the American Sugar Refining Company, New York, had been elected as founder members of the foundation. The following have been elected sustaining members: Gerber Products Company, Fremont, Mich.; Golden State Company, Ltd., San Francisco; Chr. Hensen's Laboratory, Inc., Little Falls, N. Y.; McCormick & Co., Baltimore; Minnesota Valley Canning Company, Le Sueur, Minn., and the Drackett Company, Cincinnati. The Great Atlantic & Pacific Tea Company also have made a substantial donation to the foundation. Mr. R. Douglas Stuart, Chicago, trustee of the foundation, presided at the meeting November 12. Charles G. King, Ph.D., New York, scientific director of the foundation, presided at the afternoon program, the speakers at which included Icie G. M. Hoobler, Ph.D., Detroit, on "Explorations in Human Nutrition"; Dr. Morris Fishbein, Editor of THE JOURNAL, "Medical Aspects of Our Food Supply"; Col. Rohland A. Isker, Q. M. C., U. S. Army, "Nutrition and the Armed Forces," and Roy C. Newton, Ph.D., Chicago, "Fundamental Research in the Food Industry of Tomorrow." With Mr. George A. Sloan, New York, presiding, Sir John B. Orr, director of the Rowett Research Institute, Aberdeen, England, and Karl T. Compton, LL.D., president, Massachusetts Institute of Technology, Cambridge, spoke at the dinner session.

CORRECTION

Examinations in Obstetrics and Gynecology.—The American Board of Obstetrics and Gynecology announces that the next written examination and review of case histories (Part I) for all candidates will be held in various cities of the United States and Canada on February 13. THE JOURNAL, November 7, page 777, erroneously reported that this examination would be held in November. The Part II examination will be held in Pittsburgh, May 19-25.

Recommendations Concerning Venereal Disease.—In the article by Dr. Otis L. Anderson and others concerning "Recommendations to State and Local Health Departments for a Venereal Disease Control Program in Industry" in THE JOURNAL, November 14, on page 830, second column, under the heading "Employment Policy," item 3 should read "That, when syphilis exists in a latent stage, employment should not be delayed or interrupted."

Foreign Letters

LONDON

(From Our Regular Correspondent)

Oct. 24, 1942.

Treatment of the "Compression Syndrome"

As reported in a previous letter (THE JOURNAL, June 28, 1941), the bombing of our civilian population from the air led to the discovery of a new pathologic condition—renal failure after crushing of the limbs by fallen débris. In a discussion at the Royal Society of Medicine it was suggested that the breakdown of autolytic products from dead or dying muscle seemed to be the main factor in damaging the kidneys. Not only were the cells of the tubules poisoned, but myohemoglobin was precipitated in the tubes. Among other measures early diuresis by means of abundant warm drinks was suggested as important. A quite different view of the pathology and treatment is now brought forward.

From the wards of the Middlesex Hospital and the attached Courtauld Institute Mr. D. H. Patey, surgeon, and Dr. J. D. Roberston, clinical chemical pathologist, bring forward the following view: On rescue the victim may look surprisingly well, but hours later he becomes gravely ill from shock, and, if this is overcome, within about twenty-four hours fresh anxiety arises from hematuria and low urinary output. Despite measures to promote diuresis, the oliguria increases to fatal anuria. The limb that has been pinned down becomes swollen and hard with edema and is partly or completely paralyzed by nerve compression. The writers object to the term "crush syndrome," for crushing and pulping of the tissues is not a striking feature. It is much more typical for the limb to show no evidence of damage except some cutaneous abrasions. A more accurate term would be "compression syndrome." The cause of the syndrome has given rise to much speculation. Most theories incline to the view that the syndrome is due to a toxin produced by the damaged tissues. But treatment based on this has been disappointing. In March 1941 the writers suggested that the cause of the syndrome was loss of blood constituents from the circulation into the tissues of the limb, the capillaries of which had lost their function in consequence of the long compression. But while unable to give a complete explanation of the renal phase they decided to introduce a new treatment based on their conception of the problem—restoring extravasated fluid to the circulation by intermittent pressure up to 60 mm. of mercury applied to the limb by a specially made large blood pressure cuff firmly bandaged and connected with a passive vascular exercise motor. The advice to "apply a firm bandage" is not enough. Trials showed that with different types of bandage applied in different ways a wide variety of pressure readings were obtained, varying from ineffective to dangerous pressure. They use an elastic web bandage. How long the bandage should stay on will have to be determined by experience. At present it seems that it should remain for some days.

The writers have treated some cases successfully by this method. Strong experimental support is given by a paper by Duncan and Blalock in the April issue of the *Annals of Surgery*, who produced in dogs a similar syndrome. If the affected limbs were immediately placed in a pneumatic cuff with a pressure of 40 mm. of mercury 75 per cent of the animals recovered, whereas in the control series the figure was only 5 per cent.

Anemia in Hospital Nurses on Wartime Diet

In connection with an article by Helen M. M. Mackay, R. H. Dobbs, Lucy Wills and Kaitilin Bingham, which appeared in the *Lancet*, July 11, showing the existence of low grade anemia in women and children on wartime diet, which is attributed to iron deficiency in the diet, Dr. Helen P. Wright (*ibid.*, August 1) has published a communication on this anemia in nurses. She made a survey of the hemoglobin of 100 day and 25 night nurses at a base hospital of the Emergency Medical Service and confirms the findings of Mackay and her collaborators. The average hemoglobin, estimated by the Haldane method, for the day nurses was 85.2 and for the night nurses 86 per cent. In the whole series 58 per cent had hemoglobin levels below the lower limit of normality (90 per cent), while of these over a fourth were below 80 per cent. The average age of the nurses examined was 23 years. The menstrual history revealed irregularity beyond the normal physiologic variation in 29 per cent; amenorrhea and menorrhagia were present in about equal numbers. Fourteen ward sisters, whose average age was 29, showed a higher average hemoglobin level than the nurses; their average was 91.4.

Dr. Wright concludes that low grade anemia is common in the nursing profession at the present time. These young women work ten hours a day, often under trying circumstances. She agrees with the conclusion of the article as to the dietary nature of the anemia and the suggestions that iron fortified foods should be provided and that institutional diets should be under constant review in wartime. In the article referred to the deficiency of iron in the diet was connected with a low protein content, particularly animal protein. This is due to the war. It has been shown in previous letters to THE JOURNAL that the general health of the population is good in spite of restrictions, and this is still true. The anemia now described appears to be the first detrimental effect to be traced to the restrictions of rationing. But it should be remembered that some degree of anemia was not uncommon in women and children before the war.

Club for American Nurses in London

A club for American nurses has been opened in London. It will be the center for nurses who are in London on leave or are waiting to be posted. It will fulfil the same function as other clubs which have already been opened for the American fighting services and be a center of information and recreation. At the opening ceremony a broadcast was made to America by Mrs. Biddle, who interviewed two of the nurses at the microphone, and by Mrs. Churchill, who said "It is a rare opportunity for women of our two countries to get together and form such links of friendship and confidence as may endure from generation to generation." Captain Margaret E. Aaron, superintendent of nurses in the European theater of operations, replied on behalf of the nurses. Mr. W. E. Stevenson of the American Red Cross and Colonel Horley, Surgeon General of the American forces in this country, also spoke.

The club will eventually consist of seven houses in Charles Street. The first section, which was opened, contains the information bureau, sitting room, library, ball room, table tennis and card room, as well as dormitory space for fifty nurses. There is also a dining room to be opened soon as a restaurant serving meals on the cafeteria system and specializing in American dishes.

A Nutrition Council

A controversy is being waged in the *Times* by the leaders of the medical profession as to how the proposed Nutrition Council, described in a previous letter, should be formed. Sir Charles Wilson, president of the Royal College of Physicians, thinks that it should not be a purely medical body and that it should be set up by the Food Investigation Board. Lord Dawson suggests that the Medical Research Council is a suitable body on which to base the new organization. Its duties are not exclusively concerned with medical research and its work overflows national boundaries. The latter point is important, as the Nutrition Council should direct the relief of the oppressed peoples of Europe when the nazi scourge has been crushed. Of the Medical Research Council's varied staff of experts 60 per

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cent have no medical qualifications. Its various committees cover a wide field besides medical research in the restricted sense. An investigation into the health of miners involved examinations of the men and their working environment and required the cooperation of mining experts, chemists and geologists. Its industrial health research board held an inquiry into the personal factor in accidents, for which a membership of eleven included experts on physiology, psychology, chemistry, health, vital statistics and two members of industrial experience.

In nutrition the work of the council is noteworthy. Sir Henry Dale, pharmacologist, who is president of the Royal Society, has until recently been director of the national institute at Hampstead, and his successor is a distinguished biochemist. From this institute have emerged many additions to our knowledge of nutrition and its applications. As far as concerns the empire, the council works in close cooperation with the dominions and the Colonial Office. Its staff has played a prominent part in the production of the "Report on Nutrition in the Colonial Empire." In the international sphere the council has done important work. One of its members was chairman of the International Technical Commission on Nutrition, which laid down the dietetic requirements according to age and work and as affected by pregnancy and lactation. Another example of team work was the International Committee on Vitamin Standardization, whose activities have been continuous since 1931. During the war two new vitamin standards, E and B_1, have been adopted. In the International Commission on the Relation of Nutrition, Health, Agriculture and Economic Policy the Council took a prominent part.

The Teaching at Guy's Hospital

The depletion by the war of the teaching staff of Guy's Hospital has created a problem. A prewar registrar of that famous hospital submits in a letter to *Guy's Hospital Gazette* that the fame of Guy's as a great teaching hospital has always been due in large measure to the noncramming methods employed. The Guy's student has always been taught to observe and come into close contact with patients and has been given the opportunity of studying and even treating cases himself to an extent unheard of in other hospitals. Formal teaching is reduced to a minimum, on the assumption that theoretical knowledge of clinical medicine and surgery can be obtained perfectly well from textbooks. The "cramming" system, practiced in some other medical schools, consists in numerous systematic lectures, demonstrations, teaching rounds, revision classes and so on, which leave little time for private clinical studies. While excellent for success in examinations, it does not fit a man nearly so well for the practice of medicine as does the Guy's system.

The prewar registrar states that shortly before the war more and more of the "cramming system" was being gradually introduced into the teaching methods of Guy's, for reasons which do not concern him at the moment. The effect on many students was unfortunate. They felt that they were having so much teaching that little or no effort was required on their part, and it became rarer and rarer to find students in the wards or outpatient departments when such attendance was required of them. Indeed, amid the welter of lectures, classes, teaching rounds and revision demonstrations they had little time to spare for private clinical work—that self teaching by constant personal contact with patients which is the essence of the Guy's teaching system. In addition, a feeling grew up that it was the duty of the medical school to get them through their final examinations, and they were both surprised and hurt when it was suggested that their failure to pass was due to their lack of initiative. At that time he and several of his colleagues on the junior staff deplored what was then only a tendency to the cramming system and felt that Guy's teaching was being jeopardized, though not to a serious extent. The students were in danger of being overtaught. He suggests a reduction in the amount but not in the standard of teaching. Good teaching in clinical medicine should seek to guide and encourage the student to make his own observations and so develop his clinical sense and should never ape the textbook or degenerate into mere "spoon feeding." Such a method of teaching throws far more work and responsibility on the student, and the lazy man loathes it. But the keen and conscientious student finds that it well repays him in after years.

BRAZIL

(From Our Regular Correspondent)

Oct. 1, 1942.

Transmission of Leprosy by Ticks

Dr. H. Souza Araujo of the Oswaldo Cruz Institute has carried out some experiments that have perhaps demonstrated that leprosy can be transmitted through the bite of common ticks. Starting from the fact published by Max Rudolf in *Brazil-Medico* (1918) that pupae of Amblyomma cayennensis, thirteen days after the last bite of patients affected with leprosy, showed live bacilli in the contents of the intestine, Araujo repeated the same experiments and ascertained that such bacilli, seven days after the last bite, were poorly stained, vacuolated and perhaps in the course of digestion. After forty-eight hours of feeding on patients with active leprosy the pupae of the same species of tick presented, in more than 60 per cent of the specimens, homogeneous bacilli, well stained by the Ziehl-Neelsen method, forming bundles and small globi, with all the characteristics of Mycobacterium leprae. In a second note just published in the *Memorias* of the Oswaldo Cruz Institute Araujo describes his new experiments with a cattle tick, Boophilus microplus. Several specimens of this tick were fed for a few days on active patients of the St. Roque Leprosarium in the state of Paraná and sent to Dr. Araujo at the Oswaldo Cruz Institute. Seven days after the last blood meal the contents of the intestines of the ticks showed strongly positive acid fast bacilli. In the same note Dr. Araujo describes the results of the cultures from the material of the intestines of the Amblyomma referred to in the first note. The cultures in Loewenstein medium are pure and the bacilli are strongly acid fast in a subculture. The culture material is not rich enough to make possible the inoculation in animals, which will be done in the near future.

Sterilization of Leprous Patients

Before the Sociedade Paulista de Leprologia, Drs. Luis Batista and Luis Marino Bechelli discussed the sterilization of leprous patients. They presented the following conclusions:

1. Sterilization for eugenic purposes has no scientific foundation, for the infection is not transmitted by the germinative and congenital routes.

2. Sterilization with prophylactic intent presents so many difficulties that its application is impracticable. Besides this, it must be considered that the leprous male has a high index of sterility.

3. Sterilization has serious drawbacks, for it would cause great deprivation and dissemination of venereal diseases in leprous settlements and this menace would keep patients out of the leprosaries, making their entrance difficult, and so the prophylactic campaign against leprosy would be prejudiced.

Injections of Heat Killed BCG in Normal Children

Since several authors (Sayé, Saenz, Sayago and others) have described human conditions closely related to the latent allergy of tuberculous guinea pigs (after Willis), an investigation has been conducted by A. De Assis in Rio de Janeiro to develop a standard technic for routine use in this field. Starting from the belief that the primary mobilization of the specific allergy depends rather on the chemical nature of the tubercle bacillus

than on its surviving capacity in the animal tissues, heat killed BCG bodies were used to arouse the tuberculin hypersensitiveness of the organisms that could be considered in the state of latent allergy. In order to avoid any mistake regarding the specific character of the local and sensitizing effects of the bacillary bodies, 81 nontuberculous children were tested intradermally with 0.1 mg. of heat killed BCG (in 0.1 cc.) and kept thereafter under observation for some months. Since all the children were always living in nontuberculous environments and all of them failed to show any clinical or roentgenologic evidence of an eventual infection with virulent tubercle bacilli, the reactions following the BCG inoculation could be correctly ascribed to the latter. The author has been able to register four different types of reactions: (*a*) 36 children remained practically unaffected by the BCG injection, showing only a slight noncaseous papule of 5 mm. diameter at the seat of the inoculum as long as their follow-up lasted (one hundred and eight days), and none of these children became allergic; (*b*) 15 children failed to present any noticeable reaction around the inoculum but all of them reacted to intradermal tests with 2 mg. of old tuberculin (2 cases early in the second week); (*c*) 6 children presented lately (after the second week) caseous changes at the seat of their inoculum, as well as a well defined local reaction, but remained nonreactors; (*d*) 24 children showed both definite caseous local changes and a clearcut tuberculin hypersensitiveness, in 6 cases the latter appearing early in the second week. Therefore it is possible to conclude that: 1. The intradermal inoculation of heat killed BCG in nontuberculous children failed to produce tuberculin hypersensitiveness in 51.9 per cent of the cases, while in the remainder positive tuberculin tests could eventually be found early in the course of the second week. 2. Caseous changes of the local BCG lesions may occur in about 37 per cent of the cases as the primary result of the introduction of dead bacterial bodies into the skin cells. These changes occur always after the second week and are quite different from the so-called Koch's phenomenon, in some cases being entirely different from the allergy changes, the latter seeming to be rather coincidental to them in all other instances.

Rural Tuberculosis in Brazil

The *Arquivos de Higiene* has published a contribution from Dr. Cesar Araujo on rural tuberculosis in the state of Bahia. Under the direction of Dr. Araujo of the Bahia State Department of Health an investigation is being carried out to ascertain the rate of infection and the rates of morbidity and mortality from tuberculosis, besides many details in connection with that rural population. Bahia lies entirely in the tropical zone of Brazil and has the highest percentage of Negro population, as it was the center of African immigration during the sixteenth, seventeenth and eighteenth centuries. The Pirquet and Mantoux tests (1:100 and 1:10) are being used extensively, but the present contribution includes only the results of thirty-one rural areas, where 7,351 persons have been tested. Of the thirty-one areas investigated, eight have a comparatively low mortality rate from tuberculosis (between 28 and 92 per hundred thousand of population), sixteen have a high mortality rate (between 114 and 199) and seven have a very high rate (between 201 and 352). This total of 7,351 persons is made up of 3,320 males and 4,031 females; 2,129 are white and 5,222 are Negro. As for the age groups, 1,466 were under 9 years, 2,673 from 10 to 19, 1,642 from 20 to 29, 817 from 30 to 39, 444 from 40 to 49 and 309 of 50 years and over. The total positivity of the Pirquet test, performed on all 7,351 persons, was 19.7 per cent; the Mantoux test 1:100, performed on 5,898 persons, was positive in 42.8 per cent, and the Mantoux 1:10, performed on 3,253 persons, was positive in 26.0 per cent. The infection rate, as expressed by the tuberculin tests, showed an average of 56.6 per cent for males and 65.6 for females, 59.3 per cent for white persons and 68.5 per cent for Negroes. As for age, there was no significant difference between the two sexes within each age group, and the incidence of positivity was 40.3 per cent for 0-9 years, 65.4 per cent for 10-19 years, 77.4 per cent for 20-29 years, 78.9 per cent for 30-39 years, 78.3 per cent for 40-49 years and 73.2 per cent for 50-years and over. Within the groups of 0-9 and 10-19 years 20.8 per cent were positive in 134 infants below 1 year, 33.9 per cent in 560 preschool children and 55.1 per cent in 1,981 school children. To give a basis for comparison, it is interesting to point out that in the great cities like Rio de Janeiro and São Paulo the average positivity of the tuberculin tests is 9.5 per cent below 1 year, 18.7 per cent in the preschool age and 27.0 per cent in the school age. The total positivity rate varied in the thirty-one rural areas of the state of Bahia mainly in accordance with the different social groups, apparently more correlated with the social and vocational differences than with the degree of rurality of the environment. The interior of Bahia, as the inland districts of the other northern states of Brazil, is being progressively infected with tuberculosis, through the influence of the interhuman relations with the cities of the Atlantic littoral, the afflux of urban tuberculous patients in search of a drier and cooler climate, the low standard of living, the rural endemic diseases (hookworm disease, malaria), the lack of health education and deficient medical assistance.

Surgical Treatment of Varicocele

In a recent paper Dr. Eurico Branco Ribeiro, director of São Lucas Sanatorium in São Paulo, submitted a surgical method of treatment for painful varicoceles, with ptosis of the testis and glandular atrophy or in cases in which the disease may cause occupational disturbance. Dr. Ribeiro modified the method described by Zephirino do Amaral, which is widely employed by Brazilian surgeons.

The new technic is as follows:

1. The usual incision for inguinal hernia is made large enough to expose the aponeurosis of the external oblique, the spermatic cord and the external inguinal ring.

2. The spermatic cord is freed from the external ring to near the testis, which is gently pulled from the scrotum.

3. Incision of the infundibuliform fascia and careful dissection of the spermatic vessels, from the vas deferens, are done.

4. The vas deferens is laid down, while the other elements of the spermatic cord—veins, arteries and nerves—are arched over the aponeurosis of the external oblique and here fixed by the plication of the same aponeurosis held in place by chromic catgut sutures. This results in a tunnel, which shelters the vessels and nerves of the spermatic cord, thus avoiding stasis of the blood.

5. The testis is kept in the right place by suturing the tunica vaginalis in the lowest part of the aponeurosis of the external oblique muscle. Another means of fixation is formation of the previously mentioned tunnel.

6. The skin is sutured.

Dr. Ribeiro stated that the first patients operated on by this method five years ago are in excellent condition.

Studies on Plasma

An experimental study on plasma by Drs. Carlos Schelini, Italo Martinari, Toledo de Carvalho and Paca de Azevedo in the Institute Pinheiros of São Paulo was reported before São Lucas Society recently. They reviewed the history of transfusion and pointed out the advantages of plasma over all the other blood substitutes. They reported a comparative study on blood and plasma in dogs submitted to hemorrhagic shock. They concluded that plasma quickly restores arterial pressure in dogs subjected to hemorrhagic shock. It is effective even when only 33 per cent of the quantity of the blood lost is employed. Plasma, they said, is an effective substitute for blood in cases of hemorrhagic shock.

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Deaths

Luther Crouse Peter ● Philadelphia; University of Pennsylvania Department of Medicine, Philadelphia, 1894; Medico-Chirurgical College of Philadelphia, 1896; emeritus professor of ophthalmology at the Medico-Chirurgical College, Graduate School of Medicine, University of Pennsylvania; professor of ophthalmology at the Temple University School of Medicine from 1917 to 1930; specialist certified by the American Board of Ophthalmology, past president and formerly member of that board; member and past president of the American Academy of Ophthalmology and Otolaryngology; member of the International Congress of Ophthalmology and in 1922 secretary-treasurer; member of the American Ophthalmological Society and the Association for Research in Ophthalmology, Inc.; fellow of the American College of Surgeons, the Oxford (England) Congress of Ophthalmology, and the College of Physicians of Philadelphia; consulting ophthalmologist to the Friends Hospital, Graduate Hospital of the University of Pennsylvania, the Memorial Hospital, Roxborough, and the Rush Hospital for Consumption and Allied Diseases; in 1934 received the honorary degree of doctor of science from the Susquehanna University, Selinsgrove, Pa., and in 1938 the honorary degree of doctor of laws from Gettysburg (Pa.) College; author of "The Principles and Practice of Perimetry," the fourth edition published in 1938, and "The Extra-Ocular Muscles," the third edition published in 1941; aged 73; died, November 12, in the Graduate Hospital of the University of Pennsylvania.

David Sweeney Hillis ● Chicago; Northwestern University Medical School, Chicago, 1898; professor of obstetrics at his alma mater; specialist certified by the American Board of Obstetrics and Gynecology, Inc.; member of the Central Association of Obstetricians and Gynecologists; fellow of the American College of Surgeons; past president of the Chicago Gynecological Society; served as a lieutenant commander in the Medical Corps, U. S. Naval Reserve, during World War I and was retired with the rank of captain; was responsible for the development of the DeLee-Hillis stethoscope; member of the advisory staff of the Chicago Memorial Hospital; chairman of the obstetrical department of the Cook County Hospital and attending obstetrician to the Passavant Memorial Hospital, where he died, November 9, of carcinoma of the lung, aged 69.

Edward Charles Fabre-Rajotte, San Francisco; McGill University Faculty of Medicine, Montreal, Que., Canada, 1899; member of the California Medical Association and the Pacific Coast Oto-Ophthalmological Society; member of the faculty of the University of Paris, France, 1911-1912; served with the U. S. Volunteer Medical Service Corps in 1918; awarded the Chevalier of the Legion of Honor of France in 1935; chief surgeon of the eye, ear, nose and throat department at the French Hospital; aged 67; died, September 14.

Henry B. Marriott, Battleboro, N. C.; University of Maryland School of Medicine, Baltimore, 1883; formerly served as mayor of Battleboro, member of the county board of commissioners and member of the county school board; member of the medical reserve corps of the U. S. Army during World War I; aged 79; died, October 24, of pneumonia.

George Ainslie Hendry, Sydney, N. S., Canada; University of Toronto Faculty of Medicine, 1935; appointed a surgeon lieutenant in the Royal Canadian Naval Volunteers Reserve, May 20, 1941; aged 31; was lost at sea when his ship, the *Ottawa*, was torpedoed by an enemy submarine, September 13.

David Jamieson, Durham, Ont., Canada; University of Toronto Faculty of Medicine, 1878; formerly chairman of the Old Age Pensions Board; represented his constituency for twenty-four years in the Ontario Legislature, four of them as speaker; aged 86; died, September 12.

Edward Palestine Hawkins, Montrose, Minn.; University of Michigan Department of Medicine and Surgery, Ann Arbor, 1897; at one time physician in charge of the Montrose Hospital; aged 79; died, September 28, of coronary thrombosis.

William Arrelious Page, Barlow, Ky.; St. Louis College of Physicians and Surgeons, 1903; member of the Kentucky State Medical Association; aged 66; died, October 22, in the Illinois Central Hospital, Paducah, of cerebral hemorrhage.

Otto Charles Sommerfield, Chicago; College of Physicians and Surgeons of Chicago, School of Medicine of the University of Illinois, 1909; on the staff of the Belmont Community Hospital; aged 56; died, October 14, of coronary thrombosis.

James P. Oldham ● San Antonio, Texas; University of Louisville (Ky.) Medical Department, 1886; past president of the Bexar County Medical Society; for many years on the staff of the Santa Rosa Hospital; aged 79; died, October 19.

Charles Malone ● Boston; Tufts College Medical School, Boston, 1902; on the staff of the Forest Hills (Mass.) Hospital; recently on the courtesy staff and formerly on the regular staff of St. Elizabeth's Hospital; aged 67; died, October 10.

Alfred Washington Westney ● Atlantic City, N. J.; Hahnemann Medical College and Hospital of Philadelphia, 1897; on the staff of the Atlantic City Hospital; aged 67; died, October 12, in Northfield of coronary occlusion.

Frank Anthony Pagliuca, Boston; Tufts College Medical School, Boston, 1906; member of the Massachusetts Medical Society; aged 71; died, September 18, in the Boston City Hospital of cirrhosis of the liver and myocarditis.

Louis Anthony Bontempo, Aliquippa, Pa.; Rush Medical College, Chicago, 1937; eye, ear, nose and throat resident at the Eye and Ear Hospital, Pittsburgh, from 1937 to 1940; aged 31; died, October 9, of pulmonary tuberculosis.

Paris T. Carlisle, Frederica, Del.; University of Pennsylvania Department of Medicine, Philadelphia, 1887; aged 78; died, August 3, in the Pennsylvania Hospital, Philadelphia, of renal calculi and carcinoma of the bladder.

James Monroe Matthews, Morrilton, Ark.; Memphis (Tenn.) Hospital Medical College, 1910; member of the Arkansas Medical Society; aged 66; died, September 25, of septicemia and lobar pneumonia.

Albert L. Bowman, Ottawa Hills, Ohio; Toledo Medical College, 1896; formerly served as coroner of Ottawa County; aged 77; died, October 14, in Toledo of cardiovascular renal disease with cerebral hemorrhage.

Oliver Benjamin Yarnell, Wenona, Ill.; Keokuk (Iowa) Medical College, College of Physicians and Surgeons, 1902; member of the Illinois State Medical Society; aged 65; died, October 24, in Rochester, Minn.

Joseph Octave Ernest Prud'homme, Montreal, Que., Canada; Laval University Medical Faculty, Montreal, 1919; chairman of the hospital medical board of the Hotel Dieu; aged 49; died, September 2.

Carl H. Thomsen, Dolton, Ill.; Northwestern University Medical School, Chicago, 1900; aged 69; died, October 22, in St. Luke's Hospital, Chicago, of peritonitis following an abdominal operation.

John M. Johnson ● Hartington, Neb.; John A. Creighton Medical College, Omaha, 1915; owner of St. John's Hospital; aged 67; died, October 17, in St. Vincent's Hospital, Sioux City, Iowa, of hemiplegia.

Jefferson M. Denby, Carter, Okla.; University of Nashville (Tenn.) Medical Department, 1905; member of the Oklahoma State Medical Association; aged 65; died, August 22, in San Bernardino, Calif.

Morrison Archible Taylor, Estherville, Iowa; State University of Iowa College of Homeopathic Medicine, Iowa City, 1897; aged 84; died, October 17, in Liberty, Mo., of organic heart disease.

Isaac Daniel Nolen, Newsite, Ala.; Louisville (Ky.) Medical College, 1892; member of the Medical Association of the State of Alabama; aged 72; died, October 3, of cerebral hemorrhage.

Jefferson Davis Walker, Denver; Kansas City (Mo.) Medical College, 1888; also a druggist; aged 81; died, October 10, in the Denver General Hospital of cerebral vascular accident.

Daniel F. Moorer, St. George, S. C.; Medical College of the State of South Carolina, Charleston, 1874; aged 91; died, October 11, of arteriosclerosis, cerebral thrombosis and pneumonia.

Bryan Lee Mitchell, Wilmette, Ill.; Rush Medical College, Chicago, 1926; served during World War I; on the staff of St. Francis Hospital, Evanston; aged 45; died suddenly, October 29.

John Ferguson, Mount Forest, Ont., Canada; University of Toronto Faculty of Medicine, 1903; for many years medical health officer in Kincardine; aged 66; died suddenly, September 15.

Oswald Edward Kennedy, Landis, Sask., Canada; Queen's University Faculty of Medicine, Kingston, Ont., 1916; aged 50; died suddenly, August 3, as the result of a fall in his office.

Milton Harvey Evans, Joplin, Mo.; University of Wooster Medical Department, Cleveland, 1890; Rush Medical College, Chicago, 1891; aged 81; died, October 6, of myocarditis.

Robert Lee Cater, Perry, Ga.; Jefferson Medical College of Philadelphia, 1888; member of the Medical Association of Georgia; aged 76; died, September 16, of myocarditis.

Benjamin Silas Potter, Artesia, Calif.; Indiana Medical College, School of Medicine of Purdue University, Indianapolis, 1906; aged 68; died, September 16, of heart disease.

Henry Stanley Riddle, Camden, N. J.; Medico-Chirurgical College of Philadelphia, 1904; recently a member of the draft board; aged 62; died, October 19, of heart disease.

Nathan Joseph Cuden, Philadelphia; Jefferson Medical College of Philadelphia, 1933; aged 35; died, August 4, of pneumonia and hypertensive cardiovascular disease.

Geza Bukki, Pittsburgh; Magyar Királyi Pázmány Petrus Tudományegyetem Orvosi Fakultasa, Budapest, Hungary, 1895; aged 71; died, August 11, of coronary occlusion.

Olive B. C. McCurdy, Indianapolis; Central College of Physicians and Surgeons, Indianapolis, 1891; aged 75; died, September 21, in the Irvington Sanitarium.

Jacques Conrad Saphier, Brooklyn; Cornell University Medical College, New York, 1940; diplomate of the National Board of Medical Examiners; formerly assistant resident at the Bellevue Hospital, New York; lieutenant (j. g.) U. S. Naval Reserve, assigned to the Marine Corps; aged 27; was killed in action at Guadalcanal of the Solomon Islands, August 21.

KILLED IN ACTION

Lieut. Jacques Conrad Saphier, M. C., U. S. N. R., 1915-1942

Robert Abraham Maitland Cook, Calgary, Alta., Canada; Trinity Medical College, Toronto, Ont., 1903; served overseas during World War I; aged 62; died, August 28.

Harold Nelson O'Brien, Fullerton, Calif.; Milwaukee Medical College, 1900; served during World War I; aged 65; died, September 28, of acute coronary occlusion.

W. R. L. Dwyer, New Plymouth, Ohio; Medical College of Ohio, Cincinnati, 1883; aged 81; died, September 24, in the Athens (Ohio) State Hospital of arteriosclerosis.

Jacob Hyman, Los Angeles; Ohio State University College of Medicine, Columbus, 1913; also a minister; aged 71; died, September 9, of carcinoma of the stomach.

Judson Thomas Williams, Denver; Johns Hopkins University School of Medicine, Baltimore, 1919; aged 50; was found dead, September 25, of coronary occlusion.

John Jamison Laird ● Blackcreek, Wis.; Rush Medical College, Chicago, 1904; aged 63; died, October 16, in Appleton of cerebral hemorrhage and diabetes mellitus.

Norman John Claude Carter, Toronto, Ont., Canada; University of Toronto Faculty of Medicine, 1941; aged 33; died, October 8, in St. Michael's Hospital.

John De Mott Ten Eyck, Franklin Park, N. J.; College of Physicians and Surgeons, Baltimore, 1895; aged 76; died, October 10, of amyotropic lateral sclerosis.

Harry Robert Gourley, Punxsutawney, Pa.; Ohio Medical University, Columbus, 1902; aged 70; died, October 20, in the Adrian Hospital of cerebral hemorrhage.

Oliver Ringwalt Klugh, Harrisburg, Pa.; Jefferson Medical College of Philadelphia, 1889; aged 75; died, September 14, of arteriosclerotic coronary artery disease.

Lewis Hartley Lewis, Oshawa, Ont., Canada; University of Toronto Faculty of Medicine, 1928; member of the board of education; aged 41; died, September 25.

Dennis J. Johnson, Seagrove, N. C.; University of Tennessee Medical Department, Nashville, 1895; aged 73; died, September 4, probably of heart disease.

Thomas Lea Brooks, Oceana, Va.; University College of Medicine, Richmond, 1899; member of the Medical Society of Virginia; aged 65; died, August 21.

Lionel Louis Albert, Yonkers, N. Y.; Tufts College Medical School, Boston, 1912; aged 52; died, September 6, in the Yonkers Professional Hospital.

Henry Carroll Conley, Boone, Iowa; University of Maryland School of Medicine, Baltimore, 1885; aged 80; died, September 26, of cerebral hemorrhage.

Elbert Maltby Barnes ● Gilman, Iowa; Northwestern University Medical School, Chicago, 1901; aged 67; died, September 9, of cerebral hemorrhage.

Ephraim D. Rice, Flint, Mich.; Detroit College of Medicine, 1894; member of the Michigan State Medical Society; aged 70; died, August 21, in Mio.

Samuel Jesse Petty, Decatur, Texas; Fort Worth School of Medicine, Medical Department of Fort Worth University, 1901; aged 66; died, August 16.

Emile S. Silbernagel, Vancouver, B. C., Canada; University of Pennsylvania Department of Medicine, Philadelphia, 1902; aged 64; died October 16.

George W. Cardwell, Elizabeth City, N. C.; Leonard Medical School, Raleigh, 1899; aged 71; died, September 27, of carcinoma of the prostate.

Newell E. Armstrong, Booneville, Ark.; University of Arkansas School of Medicine, Little Rock, 1902; aged 74; died, September 15.

Monroe Joseph Garrison, Chicago; Loyola University School of Medicine, Chicago, 1933; aged 33; died, September 17, in St. George's Hospital.

Peter Christian Gilberson, Pasadena, Calif.; Milwaukee Medical College, 1895; aged 78; died, October 6, of carcinoma of the small intestine.

Charles Edward Kernodle, Elon College, N. C.; University of Maryland School of Medicine, Baltimore, 1911; aged 63; died, October 15.

Arthur Lewis Knisely, Brownington, Mo.; Barnes Medical College, St. Louis, 1901; served during World War I; aged 69; died, October 12.

Ladislaus M. Ottofy, Clayton, Mo.; Homeopathic Medical College of Missouri, St. Louis, 1888; aged 77; died, October 15, of heart disease.

Leo Reich, Cleveland; Southern Medical College, Atlanta, Ga., 1895; aged 79; died, September 27, of coronary thrombosis and hypertension.

Elmer Wellington Brown, Neustadt, Ont., Canada; Western University Faculty of Medicine, London, 1911; aged 57; died, August 20.

David B. Craig, Attica, Kan.; Eclectic Medical University, Kansas City, 1908; aged 84; died, October 26, of cerebral hemorrhage.

Eugene Adolf Bergholz, Milwaukee; Rush Medical College, Chicago, 1934; aged 38; died, September 5, at his home in Wauwatosa, Wis.

William Thomas Gemmell, Stratford, Ont., Canada; Trinity Medical College, Toronto, 1903; aged 67; died, September 9.

W. A. Crook, Michigan City, Ind. (licensed in Texas, under the Act of 1907); aged 67; died, October 7, of carcinoma of the larynx.

John Peter Sinclair, Gananoque, Ont., Canada; University of Toronto Faculty of Medicine, 1894; aged 72; died, September 12.

William L. Carroll, Struthers, Ohio; Baltimore Medical College, 1894; aged 77; died, September 22, of arteriosclerosis.

John Baird ● Superior, Wis.; Trinity Medical College, Toronto, Ont., Canada, 1888; aged 82; died, October 3.

James F. Blanchard, Creal Springs, Ill.; Eclectic Medical Institute, Cincinnati, 1881; aged 86; died, September 26.

James Wilson Fox, Brighton, N. Y.; University of Buffalo School of Medicine, 1896; aged 76; died, September 22.

Emile Dehaye Saint Cyr, Chicago; Rush Medical College, Chicago, 1888; aged 76; died, August 26.

J. C. Frizzell, Bradford, Ark. (licensed in Arkansas in 1903); aged 67; died, October 10.

J. Frank Pairet, Levy, Ark. (licensed in Arkansas in 1903); aged 71; died, September 23.

V 12 1942

Correspondence

A REGISTRY OF OVARIAN TUMORS

To the Editor:—At its recent annual meeting the American Gynecological Society undertook the sponsorship of an American Registry of Ovarian Tumors and appointed from its fellows a committee of five gynecologic pathologists to carry on this work.

The need and wisdom of such a project must be obvious to every gynecologist, for no problem of pathology is in greater need of clarification than this. No entirely satisfactory classification of ovarian tumors exists, largely because of our ignorance of the histogenesis of many of these growths. Even in tumor types which are fairly well defined, such as the papillary growths, prognosis is often difficult because of the not infrequent lack of parallelism between clinical and histologic malignancy, and mistakes in both diagnosis and prognosis are frequent. Again, tumors are not infrequently encountered concerning the nature of which even expert pathologists cannot be certain. Finally, a whole group of ovarian tumors of rather special histogenesis and microscopic appearance has been described in recent years, and there are many pathologists who, because of the relative rarity of these tumors, have had no opportunity of familiarizing themselves with their histologic characteristics.

Instead of limiting its study to a registry of rare ovarian tumors, comparable perhaps to that which has been employed so successfully by general pathologists with bone sarcoma, the committee has decided to widen its scope to include ovarian tumors of all varieties. It therefore seeks the cooperation of all gynecologists and pathologists in this ambitious project and appeals to them for cooperation by seeing to it that properly prepared slides of all ovarian tumors, more particularly those of unusual or doubtful nature, be sent to this central registry for composite study by the members of the committee.

With the slides should be sent an adequate clinical history, including such essential data as the patient's age, menstrual and marital history, gynecologic examination and the operative procedure carried out, as well as a gross description of the tumor. When photographs of the latter are available, they would be welcomed. If the gross specimen or blocks of tissue are sent, they should be fixed in 10 per cent solution of formaldehyde.

It is obvious that the real value of such a study would be enormously lessened if it did not include also a study of the subsequent course of the cases, particularly in the malignant and doubtful groups of tumors. Such correlated clinical and microscopic study must be the chief hope of improving our evaluation and classification of ovarian neoplasms. To facilitate such a follow-up study the name of the attending surgeon should be included in the data.

The committee has no intention of making this a purely diagnostic service, but all those who send in slides will in due course receive reports of the diagnosis and classification arrived at by the committee. Since each slide will be studied by every member of the committee and perhaps by other pathologists as well, and since this will involve correspondence between men scattered in different sections of the country, it will be understood that such reports of findings cannot be made with great promptness.

Finally, the committee fully appreciates that many of the ovarian tumors submitted to it will be worthy of report by the referring physicians, and it need scarcely emphasize that neither the committee as a whole nor any individual member will utilize any submitted case for publication without the express permission of the referring physician. It is hoped that, as the work progresses, reports of the committee's studies will be published from time to time, but those referring cases for study will be given full credit in any such publication.

The committee feels that it has been given a great opportunity to render a worthwhile service, and it sincerely hopes that individual clinicians and pathologists in all sections of the country will feel that they too can contribute vitally in this project by developing the routine of sending slides of interesting ovarian tumors with the data indicated to the committee for study and registry. This material should be mailed to Dr. Emil Novak, Laboratory of Gynecological Pathology, Johns Hopkins Hospital, Baltimore.

EMIL NOVAK, Chairman. GEORGE H. GARDNER.
ROBERT MEYER. KARL H. MARTZLOFF.
HERBERT F. TRAUT.

FOOT BATHS FOR "ATHLETE'S FOOT"

To the Editor:—In Queries and Minor Notes in THE JOURNAL, June 27, it was stated that "a satisfactory formula for a good powder for use in the treatment of trichophytosis is sodium thiosulfate 6 Gm. and boric acid 24 Gm." I first described foot baths and this powder formula for this condition in THE JOURNAL, April 18, 1931, page 1301, and Oct. 3, 1931, page 1020. It is highly important to endeavor to eradicate as much as possible this most disabling of all foot infections. With this in mind I shall enumerate some of the advantages of both the powder and the bath:

1. The Bath: The sodium hyposulfite bath is stable. Chlorine, for example, is not. Chlorine too is an essential war chemical best used elsewhere.

My "hypo" bath can be made in any handy container: wood, metal, tile, in fact any material. The chlorine bath needs a rubber container. Many thousands of these rubber containers now being used for foot baths could be turned in for our war effort where rubber is so much more needed. Thus two war essentials, chlorine and rubber, could be salvaged.

The making of the "hypo" bath is not a procedure of chemical precision. Although I have recommended a 10 per cent "hypo" bath, I have also described that anywhere from 3 per cent up is effective. Even a very concentrated solution, though not necessary, is harmless to the skin.

Ordinary "hypo" crystals, the large commercial type, in fact the "hypo" of photography, is the kind used for these baths. The crystals are much handier and more readily transportable than the unstable 0.5 or 1 per cent chlorine solutions. Many institutions have found success with the following crude but very practical method: Use any container large enough for the immersion of both feet. Add water to reach the level of the ankle. Throw a handful or cupful of "hypo" crystals into the water.

Where the "hypo" bath is near a chlorinated swimming pool, the chlorine content of the pool is not affected (THE JOURNAL, Oct. 3, 1931) particularly where an automatic chlorine content regulator is used.

2. The Powder: The powder may be in bulk or packaged in handy sifter top containers so as to be ready for use anywhere.

Solutions are good for the feet and floors only but not for the footwear. The powder is good for all three. The footwear, which harbors the trichophyton organism, is the common cause of infection as well as reinfection.

The powder need only be sprinkled lightly on the foot and footwear but more heavily on the floors of the showers and locker rooms. It is necessary to throw only a handful or cupful of this powder on the threshold leading from the showers to the lockers. By this simple expedient with the powder or, as before mentioned, by throwing a handful of the "hypo" crystals into the foot bath, we have effective means of combating this skin disease.

To be ideal, foot hygiene should be applicable and efficacious all the way from the home guard and the rear guard to the

front line trenches. Keeping a soldier on his feet is paramount. It is therefore of greatest importance that this most prevalent and most disabling of foot diseases be conquered. That we have such simple means to do this under such varying conditions should be taken into consideration by all physicians caring for our civilians and fighting forces.

W. L. GOULD, M.D., Albany, N. Y.

Medical Examinations and Licensure

COMING EXAMINATIONS AND MEETINGS

ANNUAL CONGRESS ON MEDICAL EDUCATION AND LICENSURE

CHICAGO, Feb. 15, 1943. Sec., Council on Medical Education and Hospitals, Dr. H. G. Weiskotten, 535 North Dearborn Street, Chicago.

NATIONAL BOARD OF MEDICAL EXAMINERS EXAMINING BOARDS IN SPECIALTIES

Examinations of the Examining Boards in Specialties were published in THE JOURNAL, Nov. 21, page 984.

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MONTANA: Helena, April 6-7. Sec., Dr. Otto G. Klein, First National Bank Bldg., Helena.

NEW HAMPSHIRE: Concord, March 11-12. Sec., Board of Registration in Medicine, Dr. Deering G. Smith, State House, Concord.

NEW MEXICO: * Santa Fe, April 12-13. Sec., Dr. Le Grand Ward, 135 Sena Plaza, Santa Fe.

NEW YORK: Albany, Buffalo, New York and Syracuse, Jan. 25-28. Chief, Bureau of Professional Examinations, Mr. H. L. Field, 315 Education Bldg., Albany.

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RHODE ISLAND: * Providence, Jan. 7-8. Chief, Division of Examiners, Mr. Thomas B. Casey, 366 State Office Bldg., Providence.

SOUTH DAKOTA: Pierre, Jan. 19-20. Dir., Medical Licensure, State Board of Health, Dr. J. F. D. Cook, Pierre.

TENNESSEE: Memphis, Dec. 16-19. Sec., Dr. H. W. Qualls, 130 Madison Ave., Memphis.

TEXAS: Austin, Dec. 28-30. Sec., Dr. T. J. Crowe, 918-20 Texas Bank Bldg., Dallas.

UTAH: Salt Lake City, June. Dir., Department of Registration, Mr. G. V. Billings, 324 State Capitol Bldg., Salt Lake City.

VERMONT: Burlington, March 25-27. Sec., Dr. F. J. Lawliss, Richford.

VIRGINIA: Richmond, Dec. 8-11. Sec., Dr. J. W. Preston, 30½ Franklin Rd., Roanoke.

WASHINGTON: * Seattle, Jan. 11-13. Dir., Department of Licenses, Mr. Thomas A. Swayze, Olympia.

WEST VIRGINIA: Charleston, March 1-3. Commissioner, Public Health Council, Dr. C. F. McClintic, State Capitol, Charleston.

WISCONSIN: * Madison, Jan. 12-14. Sec., Dr. H. W. Shutter, 425 E. Wisconsin Ave., Milwaukee.

WYOMING: Cheyenne, Feb. 1-2. Sec., Dr. M. C. Keith, Capitol Bldg., Cheyenne.

* Basic Science Certificate required.

BOARDS OF EXAMINERS IN THE BASIC SCIENCES

ARIZONA: Tucson, Dec. 15. Act. Sec., Dr. Robert L. Nugent, University of Arizona, Science Hall, Tucson.

COLORADO: Denver, Dec. 16-17. Sec., Dr. Esther B. Starks, 1439 Ogden St., Denver.

CONNECTICUT: Feb. 13. Address State Board of Healing Arts, 1945 Yale Station, New Haven.

DISTRICT OF COLUMBIA: Washington, April 19-20. Sec., Commission on Licensure, Dr. George C. Ruhland, 6150 E. Municipal Bldg., Washington.

FLORIDA: DeLand, June 9. Sec., Dr. J. F. Conn, John B. Stetson, University, DeLand.

IOWA: Des Moines, Jan. 12. Dir., Division of Licensure & Registration, Mr. H. W. Grefe, Capitol Bldg., Des Moines.

MICHIGAN: Ann Arbor and Detroit, Feb. 12-13. Sec., Miss Eloise LeBeau, 101 N. Walnut St., Lansing.

MINNESOTA: Minneapolis, Jan. 5-6. Sec., Dr. J. C. McKinley, 126 Millard Hall, University of Minnesota, Minneapolis.

NEW MEXICO: Albuquerque, Feb. 1. Sec., Miss Pia Joerger, State Capitol, Santa Fe.

OKLAHOMA: Oklahoma City, May, 1943. Sec., Dr. Oscar C. Newman, Shattuck.

OREGON: Portland, Feb. 13. Sec., Board of Higher Education, Mr. Charles D. Byrne, University of Oregon, Eugene.

SOUTH DAKOTA: Sioux Falls, Dec. 4-5. Sec., Dr. G. M. Evans, Yankton.

WASHINGTON: Seattle, Jan. 7-8. Dir., Department of Licenses, Mr. Thomas A. Swayze, Olympia.

WISCONSIN: Milwaukee, Dec. 5. Sec., Prof. Robert N. Bauer, 152 W. Wisconsin Ave., Milwaukee.

Mississippi June Report

The Mississippi State Board of Health reports the written examination for medical licensure held at Jackson, June 24-25, 1942. The examination covered 12 subjects and included 96 questions. An average of 75 per cent was required to pass. Forty-five candidates were examined, 43 of whom passed and 2 failed. Twenty-two physicians were licensed to practice medicine by reciprocity. The following schools were represented:

PASSED	Year Grad.	Number Passed
College of Medical Evangelists	(1941)	1
Chicago Medical School	(1939)	1
University of Chicago, The School of Medicine	(1941)	1
University of Louisville School of Medicine	(1942, 2)	2
Tulane University of Louisiana School of Medicine	(1941), (1942, 16)	17
Washington University School of Medicine	(1942, 2)	2
Jefferson Medical College of Philadelphia	(1942)	1
University of Pennsylvania School of Medicine	(1942)	1
Medical College of the State of South Carolina	(1942)	1
University of Tennessee College of Med.	(1941, 2), (1942, 9)	11
Vanderbilt University School of Medicine	(1942)	1
Baylor University College of Medicine	(1942, 2)	2
Medical College of Virginia	(1942, 2)	2

FAILED	Number Failed
Undergraduates	2

LICENSED BY RECIPROCITY	Year Grad.	Reciprocity with
College of Medical Evangelists	(1936)	Tennessee
University of Colorado School of Medicine	(1917)	Texas
Rush Medical College	(1938)	Illinois, (1940) Kentucky
University of Illinois College of Medicine	(1938)	Illinois
University of Louisville Medical Department	(1917)	Kentucky
Louisiana State University School of Medicine	(1940)	Louisiana
Tulane University of Louisiana School of Medicine	(1918), (1938) Louisiana	
University of Nebraska College of Medicine	(1937)	Nebraska
University of Oklahoma School of Medicine	(1928)	Oklahoma
Woman's Medical College of Pennsylvania	(1936)	Kentucky
Meharry Medical College	(1941)	Tennessee
University of Tennessee College of Medicine	(1937)	Louisiana, (1932), (1940), (1941, 2) Tennessee
Vanderbilt University School of Medicine	(1909), (1938)	Tennessee
University of Virginia Department of Medicine	(1937)	Virginia
Milwaukee Medical College	(1912)	Wisconsin

Wyoming June Report

The Wyoming State Board of Medical Examiners reports 4 physicians licensed to practice medicine by endorsement on June 1, 1942. The following schools were represented:

LICENSED BY ENDORSEMENT	Year Grad.	Endorsement of
University of Kansas School of Medicine	(1939)	Kansas
University Medical College of Kansas City	(1904)	Missouri
University of Nebraska College of Medicine	(1925), (1936)	Nebraska

Bureau of Legal Medicine and Legislation

MEDICOLEGAL ABSTRACTS

Foods: Constitutionality of Municipal Ordinance Prohibiting Sale of Guaranteed Raw Milk.—The Agricultural Code of California permits the sale of five grades of market milk, namely certified, guaranteed raw, guaranteed pasteurized, grade A raw, and grade A pasteurized. An ordinance was passed by the city and county of San Francisco authorizing the sale in the city and county of only four grades, namely certified, guaranteed pasteurized, grade A pasteurized and grade B pasteurized, thus proscribing the sale of guaranteed raw milk. The Natural Milk Producers Association of California, one of the plaintiffs, was a nonprofit cooperative corporation. It was not engaged in, and did not intend to engage in, the production or sale of milk, although its members were engaged in that pursuit in California. The individual plaintiffs desired to sell guaranteed raw milk in San Francisco. Since such sales were prohibited by the ordinance, an action was instituted to enjoin its enforcement. From a judgment sustaining the validity of the ordinance, the plaintiffs appealed to the Supreme Court of California.

The plaintiffs first contended that since the ordinance prohibited the sale and distribution of two grades of milk that were approved by the state Agricultural Code, that is, guaranteed raw milk and grade A raw milk, the ordinance was in conflict with the state law and therefore invalid. Where the legislature has assumed to regulate a given course of conduct by prohibitory enactments, the court said, a municipal corporation with subordinate power to act in the matter may make such reasonable additional regulations in aid and furtherance of the purpose of the general law as seem appropriate to the necessities of the particular locality. The plaintiffs contended, however, that the Agricultural Code so completely occupied the field of regulation relating to the production, sale and distribution of milk for human consumption that there was no room for the operation of a local ordinance on the subject. With this contention the court could not agree, pointing to a provision in the section of the Code relating to milk that nothing in it was to be construed as "a limitation on the power of a municipality or county to provide for reasonable additional regulations not in conflict therewith requiring standards higher than the minimum requirements for the grades of market milk established in this division." The requirement in the ordinance that only pasteurized (certified excepted) milk could be sold was nothing more than an additional regulation, in the opinion of the court. The Agricultural Code permitted the sale of certified guaranteed milk, both raw and pasteurized, and grade A, both raw and pasteurized. The ordinance merely imposed the additional restriction that the milk, whether it is guaranteed or grade A, must be pasteurized. The plaintiffs further contended that the ordinance was discriminatory in that it prohibited the sale of any milk other than pasteurized, with the single exception of certified milk, arguing that there was no substantial difference between guaranteed raw milk and certified milk. The court thought, however, that there was a substantial and reasonable difference directly related to the public health.

While the sale and distribution of milk, the court continued, is a lawful business protected by the Constitution, it cannot be doubted that its production, distribution and sale may be strictly regulated under the police power to safeguard the public health. That other less stringent or different regulations might have sufficed did not concern the court, as that was a matter lodged within the discretion of the legislative body.

The ordinance provided that "certified milk is market milk which conforms to the rules, regulations, methods and standards . . . adopted by the American Association of Medical Milk Commissions and must bear the certificate of the Milk Commission of the San Francisco County Medical Society." The court held that this provision did not constitute an unlawful delegation of legislative power. Such a provision, observed the court, is not essentially different from a statute requiring the applicants for a license to practice medicine to produce a diploma from a medical school whose requirements are in no particular less than those prescribed by the Association of American Medical Colleges, a private organization. There was evidence to the effect that in order for a producer to obtain a permit from the Milk Commission of the San Francisco County Medical Society authorizing the sale of certified milk in the city and county he was required to permit the commission to make an inspection of his facilities and the milk produced therein and to pay certain inspection fees which the commission had fixed to cover the cost of the inspection. The plaintiffs contended that this procedure was invalid because the Milk Commission of San Francisco County Medical Society was a nongovernmental body with no authority to collect fees or to issue permits. But, said the court, the ordinance contained no provision requiring the payment of fees or other charges to the Milk Commission or to any other nongovernmental body. No payment of a fee was demanded of the plaintiffs since they had not applied for a permit to sell certified milk in San Francisco. The authority of the Milk Commission to demand and collect inspection fees in connection with the certification of milk was therefore not involved in the case.

The judgment sustaining the constitutionality of the ordinance was affirmed.—*Natural Milk Producers Ass'n v. City and County of San Francisco, 124 P. (2d) 25 (Calif., 1942).*

Optometry Practice Acts: Licentiate Entitled to a Hearing De Novo on Appeal from Revocation Order.—The California state board of optometry revoked the petitioner's certificate of registration to practice optometry, and he applied to the superior court for a writ of mandate to set aside the board's order, asking, among other things, that the superior court have a hearing and trial de novo. The court, however, considered only the record of the proceedings had before the board, denied the petitioner the right to introduce any new and material evidence and entered a judgment sustaining the board's order. The petitioner appealed to the district court of appeal, which reversed the judgment of the superior court and subsequently denied the board's petition for a rehearing. (*Laisne v. California State Board of Optometry*, 102 P. (2d) 538, J. A. M. A. 116:1738 [April 12] 1941.) The case then came before the Supreme Court of California on an appeal by the board.

The petitioner contended that he had a right to require the superior court to conduct a trial de novo in the course of which the parties would not be limited to the record made before the board. The Supreme Court pointed out that the state's governmental powers are divided into three separate departments—the legislative, executive and judicial. Under the state constitution, the judicial power is vested "in the Senate, sitting as a court of impeachment, in a Supreme Court, district courts of appeal, superior courts" and such inferior local courts as the legislature may establish. No other body may exercise statewide judicial power except as the result of constitutional amendment. If some agency with statewide jurisdiction, other than the enumerated courts, without sanction by constitutional amendment, exercises or attempts to exercise judicial power, such action is in direct violation of the constitution. The petitioner's right in this case to practice optometry was a vested property right. In the proceeding against him by the board all rights of "procedural" due process were accorded him. At the conclusion of the hearing an order was made revoking his license to practice. This would constitute an exercise of the complete judicial power contemplated by the framers of the constitution, and the petitioner would be deprived of his constitutional right, unless he had a right to go into a court of law and question the validity of that order by the introduction of any material evidence to prove that he did not commit the acts alleged.

The board contended, however, that by not providing for a court's hearing after determination by the board the legislature intended that the board's action should be final or at least that

front line trenches. Keeping a soldier on his feet is paramount. It is therefore of greatest importance that this most prevalent and most disabling of foot diseases be conquered. That we have such simple means to do this under such varying conditions should be taken into consideration by all physicians caring for our civilians and fighting forces.

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South Dakota: Sioux Falls, Dec. 4-5. Sec., Dr. G. M. Evans, Yankton.

Washington: Seattle, Jan. 7-8. Dir., Department of Licenses, Mr. Thomas A. Swayze, Olympia.

Wisconsin: Milwaukee, Dec. 5. Sec., Prof. Robert N. Bauer, 152 W. Wisconsin Ave., Milwaukee.

Mississippi June Report

The Mississippi State Board of Health reports the written examination for medical licensure held at Jackson, June 24-25, 1942. The examination covered 12 subjects and included 96 questions. An average of 75 per cent was required to pass. Forty-five candidates were examined, 43 of whom passed and 2 failed. Twenty-two physicians were licensed to practice medicine by reciprocity. The following schools were represented:

PASSED		
School	Year Grad.	Number Passed
College of Medical Evangelists	(1941)	1
Chicago Medical School	(1939)	1
University of Chicago, The School of Medicine	(1941)	1
University of Louisville School of Medicine	(1942, 2)	2
Tulane University of Louisiana School of Medicine	(1941), (1942, 16)	17
Washington University School of Medicine	(1942, 2)	2
Jefferson Medical College of Philadelphia	(1942)	1
University of Pennsylvania School of Medicine	(1942)	1
Medical College of the State of South Carolina	(1942)	1
University of Tennessee College of Med.	(1941, 2), (1942, 9)	11
Vanderbilt University School of Medicine	(1942)	1
Baylor University College of Medicine	(1942, 2)	2
Medical College of Virginia	(1942, 2)	2

FAILED	
School	Number Failed
Undergraduates	2

LICENSED BY RECIPROCITY		
School	Year Grad.	Reciprocity with
College of Medical Evangelists	(1936)	Tennessee
University of Colorado School of Medicine	(1917)	Texas
Rush Medical College	(1938)	Illinois, (1940) Kentucky
University of Illinois College of Medicine	(1938)	Illinois
University of Louisville Medical Department	(1917)	Kentucky
Louisiana State University School of Medicine	(1940)	Louisiana
Tulane University of Louisiana School of Medicine	(1918), (1938)	Louisiana
University of Nebraska College of Medicine	(1937)	Nebraska
University of Oklahoma School of Medicine	(1928)	Oklahoma
Woman's Medical College of Pennsylvania	(1936)	Kentucky
Meharry Medical College	(1941)	Tennessee
University of Tennessee College of Medicine	(1937)	Louisiana, (1932), (1940), (1941, 2) Tennessee
Vanderbilt University School of Medicine	(1909), (1938)	Tennessee
University of Virginia Department of Medicine	(1937)	Virginia
Milwaukee Medical College	(1912)	Wisconsin

Wyoming June Report

The Wyoming State Board of Medical Examiners reports 4 physicians licensed to practice medicine by endorsement on June 1, 1942. The following schools were represented:

LICENSED BY ENDORSEMENT		
School	Year Grad.	Endorsement of
University of Kansas School of Medicine	(1939)	Kansas
University Medical College of Kansas City	(1904)	Missouri
University of Nebraska College of Medicine	(1925), (1936)	Nebraska

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Bureau of Legal Medicine and Legislation

MEDICOLEGAL ABSTRACTS

Foods: Constitutionality of Municipal Ordinance Prohibiting Sale of Guaranteed Raw Milk.—The Agricultural Code of California permits the sale of five grades of market milk, namely certified, guaranteed raw, guaranteed pasteurized, grade A raw, and grade A pasteurized. An ordinance was passed by the city and county of San Francisco authorizing the sale in the city and county of only four grades, namely certified, guaranteed pasteurized, grade A pasteurized and grade B pasteurized, thus proscribing the sale of guaranteed raw milk. The Natural Milk Producers Association of California, one of the plaintiffs, was a nonprofit cooperative corporation. It was not engaged in, and did not intend to engage in, the production or sale of milk, although its members were engaged in that pursuit in California. The individual plaintiffs desired to sell guaranteed raw milk in San Francisco. Since such sales were prohibited by the ordinance, an action was instituted to enjoin its enforcement. From a judgment sustaining the validity of the ordinance, the plaintiffs appealed to the Supreme Court of California.

The plaintiffs first contended that since the ordinance prohibited the sale and distribution of two grades of milk that were approved by the state Agricultural Code, that is, guaranteed raw milk and grade A raw milk, the ordinance was in conflict with the state law and therefore invalid. Where the legislature has assumed to regulate a given course of conduct by prohibitory enactments, the court said, a municipal corporation with subordinate power to act in the matter may make such reasonable additional regulations in aid and furtherance of the purpose of the general law as seem appropriate to the necessities of the particular locality. The plaintiffs contended, however, that the Agricultural Code so completely occupied the field of regulation relating to the production, sale and distribution of milk for human consumption that there was no room for the operation of a local ordinance on the subject. With this contention the court could not agree, pointing to a provision in the section of the Code relating to milk that nothing in it was to be construed as "a limitation on the power of a municipality or county to provide for reasonable additional regulations not in conflict therewith requiring standards higher than the minimum requirements for the grades of market milk established in this division." The requirement in the ordinance that only pasteurized (certified excepted) milk could be sold was nothing more than an additional regulation, in the opinion of the court. The Agricultural Code permitted the sale of certified guaranteed milk, both raw and pasteurized, and grade A, both raw and pasteurized. The ordinance merely imposed the additional restriction that the milk, whether it is guaranteed or grade A, must be pasteurized. The plaintiffs further contended that the ordinance was discriminatory in that it prohibited the sale of any milk other than pasteurized, with the single exception of certified milk, arguing that there was no substantial difference between guaranteed raw milk and certified milk. The court thought, however, that there was a substantial and reasonable difference directly related to the public health.

While the sale and distribution of milk, the court continued, is a lawful business protected by the Constitution, it cannot be doubted that its production, distribution and sale may be strictly regulated under the police power to safeguard the public health. That other less stringent or different regulations might have sufficed did not concern the court, as that was a matter lodged within the discretion of the legislative body.

The ordinance provided that "certified milk is market milk which conforms to the rules, regulations, methods and standards . . . adopted by the American Association of Medical Milk Commissions and must bear the certificate of the Milk Commission of the San Francisco County Medical Society." The court held that this provision did not constitute an unlawful delegation of legislative power. Such a provision, observed the court, is not essentially different from a statute requiring the applicants for a license to practice medicine to produce a diploma from a medical school whose requirements are in no particular less than those prescribed by the Association of American Medical Colleges, a private organization. There was evidence to the effect that in order for a producer to obtain a permit from the Milk Commission of the San Francisco County Medical Society authorizing the sale of certified milk in the city and county he was required to permit the commission to make an inspection of his facilities and the milk produced therein and to pay certain inspection fees which the commission had fixed to cover the cost of the inspection. The plaintiffs contended that this procedure was invalid because the Milk Commission of San Francisco County Medical Society was a nongovernmental body with no authority to collect fees or to issue permits. But, said the court, the ordinance contained no provision requiring the payment of fees or other charges to the Milk Commission or to any other nongovernmental body. No payment of a fee was demanded of the plaintiffs since they had not applied for a permit to sell certified milk in San Francisco. The authority of the Milk Commission to demand and collect inspection fees in connection with the certification of milk was therefore not involved in the case.

The judgment sustaining the constitutionality of the ordinance was affirmed.—*Natural Milk Producers Ass'n v. City and County of San Francisco, 124 P. (2d) 25 (Calif., 1942).*

Optometry Practice Acts: Licentiate Entitled to a Hearing De Novo on Appeal from Revocation Order.—The California state board of optometry revoked the petitioner's certificate of registration to practice optometry, and he applied to the superior court for a writ of mandate to set aside the board's order, asking, among other things, that the superior court have a hearing and trial de novo. The court, however, considered only the record of the proceedings had before the board, denied the petitioner the right to introduce any new and material evidence and entered a judgment sustaining the board's order. The petitioner appealed to the district court of appeal, which reversed the judgment of the superior court and subsequently denied the board's petition for a rehearing. (*Laisne v. California State Board of Optometry*, 102 P. (2d) 538, J. A. M. A. 116:1738 [April 12] 1941.) The case then came before the Supreme Court of California on an appeal by the board.

The petitioner contended that he had a right to require the superior court to conduct a trial de novo in the course of which the parties would not be limited to the record made before the board. The Supreme Court pointed out that the state's governmental powers are divided into three separate departments—the legislative, executive and judicial. Under the state constitution, the judicial power is vested "in the Senate, sitting as a court of impeachment, in a Supreme Court, district courts of appeal, superior courts" and such inferior local courts as the legislature may establish. No other body may exercise statewide judicial power except as the result of constitutional amendment. If some agency with statewide jurisdiction, other than the enumerated courts, without sanction by constitutional amendment, exercises or attempts to exercise judicial power, such action is in direct violation of the constitution. The petitioner's right in this case to practice optometry was a vested property right. In the proceeding against him by the board all rights of "procedural" due process were accorded him. At the conclusion of the hearing an order was made revoking his license to practice. This would constitute an exercise of the complete judicial power contemplated by the framers of the constitution, and the petitioner would be deprived of his constitutional right, unless he had a right to go into a court of law and question the validity of that order by the introduction of any material evidence to prove that he did not commit the acts alleged.

The board contended, however, that by not providing for a court's hearing after determination by the board the legislature intended that the board's action should be final or at least that

a court should be confined to a consideration of the evidence produced at the hearing before the board. As evidence of the legislative intent in such matters, concluded the Supreme Court, reference need only be made to a recent act of the legislature proposing to voters of the state a constitutional amendment to give to the legislature the right "to confer power on administrative officers, boards or commissions to make decisions." If the proposed amendment is adopted by the people, it will authorize the legislature to confer on such administrative bodies the right to exercise judicial power. Obviously, said the court, the legislature in proposing this constitutional amendment was of the opinion that it now has no such power.

The Supreme Court, therefore, held that the superior court erred in denying the petitioner the right to introduce material and competent evidence at the trial of this action and therefore reversed the judgment of the lower court.—*Laisne v. State Board of Optometry, 123 P. (2d) 457 (Calif., 1942).*

Workmen's Compensation Acts: Operation to Provide More Serviceable Stump Following Amputation of Foot.—The claimant sustained an industrial accident to his right foot, and the anterior part of the foot was amputated including all the bones beyond the ankle joint except the two bones of the foot and heel immediately below the joint, the operation being known as Chopart's amputation. The resulting stump healed without complications and the claimant was fully compensated under the workmen's compensation act for the loss of his foot. Difficulty was experienced, however, in wearing comfortably a prosthetic appliance, and about three years later the claimant submitted to a second operation which resulted in the amputation of his leg at a point 7½ inches (19 cm.) below the knee. He then applied to the industrial commission for review of his case, contending that this second amputation was due to the industrial accident and that therefore he was entitled to compensation for the loss of part of his leg. Additional compensation was awarded, the district court sustained the award and the employer appealed to the Supreme Court of Iowa.

The court was unable to agree that the claimant was entitled to additional compensation. The only operation necessary for a complete recovery from the injury to the foot, said the court, was the first amputation, at which time there was no resulting infection and the stump entirely healed. At the time of the second operation, the claimant had lost a foot. This was the extent of his disability under the workmen's compensation act. Manifestly a second amputation was not necessary to the proper treatment of the foot. The injury to the foot did not require both operations. The sole purpose of the second operation was to give the claimant the maximum use of an artificial foot. It increased his capacity to labor and his earning power and reduced the economic handicap occasioned by the injury to his foot, and the Supreme Court, with three justices dissenting, felt that the claimant had received all the compensation to which he was entitled under the workmen's compensation act, that is, compensation for the loss of a foot. The award of additional compensation was therefore reversed.—*Schell v. Central Engineering Co., 4 N. W. (2d) 399 (Iowa, 1942).*

Drugs: Misleading Advertising of Marmola a Violation of Federal Trade Commission Act.—In 1929 the Federal Trade Commission, after hearings, found that the defendant company had used unfair methods of competition in selling a preparation called Marmola by making misleading and deceptive statements concerning its qualities as a remedy for overweight. A cease and desist order was vacated by the United States circuit court of appeals, 6th Cir., and by the United States Supreme Court (42 F. (2d) 430; 283 U. S. 643, 51 S. Ct. 587), on the ground that there was no evidence that the defendant's product was in any real competition with other similar products in the interstate market. In 1935 the commission instituted the present proceedings against the same defendant and in connection with the same product, charging unfair methods of competition in violation of the Federal Trade Commission Act. The commission found with particularity that the defendant had made many misleading and deceptive statements to further sales of Marmola; that Marmola had many active rivals for the trade of those who were interested in fat-reducing remedies, and that defendant's misleading statements had the "tendency and capacity" to induce people "to purchase and use respondent's [defendant's] . . . preparation or medicine for reducing purposes . . . in preference to and to the exclusion of the products of competitors, . . . and to divert trade to respondent from such competitors engaged in the sale in interstate commerce of medicines, preparations, systems, methods, books of instruction, and other articles and means designed, intended and used for the purpose of reducing weight." The United States circuit court of appeals, 6th Cir., again vacated the cease and desist order (123 F. (2d) 34), and the commission brought certiorari to the United States Supreme Court.

The findings of the commission were an adequate basis for its order, said the court. The evidence showed that sales of Marmola to the consuming public were made at retail drugstores through the country; that defendant distributed Marmola both to wholesalers and retailers; that the wholesalers and retailers who sold Marmola also sold numerous other remedies for taking off fat; that the essential fat-reducing element in Marmola is desiccated thyroid, which is also an element in some of the other remedies sold to the public with or without doctors' prescriptions; that many books of instruction on methods of reducing weight were sold in interstate commerce, and that the gross sales of Marmola were from $350,000 to $400,000 a year. From this and other evidence the commission concluded that numerous antifat remedies were offered for sale in the same market as Marmola and that Marmola was in active competition with them for the favor of the remedy purchasing public. It is not necessary, said the Supreme Court, that the evidence show specifically that losses to any particular trader or traders arise from the defendant's success in capturing part of the market. One of the objects of the act creating the Federal Trade Commission was to prevent potential injury by stopping unfair methods of competition in their incipiency. And, the court continued, when the commission found as it did here that misleading and deceptive statements were made with reference to the quality of merchandise in active competition with other merchandise it was also authorized to infer that trade would be diverted from competitors who do not engage in such methods.

The judgment of the circuit court of appeals was reversed with directions that the order of the Federal Trade Commission be affirmed.—*Federal Trade Commission v. Raladam Co., 62 S. Ct. 966 (1942).*

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Society Proceedings

COMING MEETINGS

American Academy of Orthopaedic Surgeons, Chicago, Jan. 17-21. Dr. Myron O. Henry, 825 Nicollet Ave., Minneapolis, Acting Secretary.

American Society of Anesthetists, New York, Dec. 10. Dr. Paul M. Wood, 745 Fifth Ave., New York, Secretary.

Annual Forum on Allergy, Cleveland, Jan. 9-10. Dr. Jonathan Forman, 956 Bryden Road, Columbus, Ohio.

Clinical Orthopaedic Society, Chicago, Jan. 18-21. Dr. Myron O. Henry, 825 Nicollet Ave., Minneapolis, Secretary.

Eastern Section, American Laryngological, Rhinological and Otological Society, Hartford, Conn., Jan. 15. Dr. Edward J. Whalen, 750 Main St., Hartford, Conn., Chairman.

Middle Section, American Laryngological, Rhinological and Otological Society, Detroit, Jan. 20. Dr. Voss Harrell, 2539 Woodward Ave., Detroit, Chairman.

Puerto Rico, Medical Association of, Santurce, Dec. 11-13. Dr. E. Martinez Rivera, P. O. Box 3866, Santurce, Secretary.

Radiological Society of North America, Chicago, Nov. 30-Dec. 4. Dr. Donald S. Childs, 607 Medical Arts Bldg., Syracuse, N. Y., Secretary.

Society for the Study of Asthma and Allied Conditions, New York, Dec. 5. Dr. W. C. Spain, 116 East 53d St., New York, Secretary.

Society of American Bacteriologists, Columbus, Ohio, Dec. 28-30. Dr. W. B. Sarles, Agricultural Hall, University of Wisconsin, Madison, Wis., Secretary.

Southern Surgical Association, Savannah, Ga., Dec. 8-10. Dr. Alton Ochsner, 1430 Tulane Ave., New Orleans, Secretary.

Current Medical Literature

AMERICAN

The Association library lends periodicals to members of the Association and to individual subscribers in continental United States and Canada for a period of three days. Three journals may be borrowed at a time. Periodicals are available from 1932 to date. Requests for issues of earlier date cannot be filled. Requests should be accompanied by stamps to cover postage (6 cents if one and 18 cents if three periodicals are requested). Periodicals published by the American Medical Association are not available for lending but can be supplied on purchase order. Reprints as a rule are the property of authors and can be obtained for permanent possession only from them.

Titles marked with an asterisk (*) are abstracted below.

American Journal of Medical Sciences, Philadelphia

204:313-468 (Sept.) 1942

Experimental Bundle Branch Block After Ablation of One or Both Ventricles. R. C. Robb and Jane Sands Robb, Syracuse, N. Y. —p. 313.

*Acute Bacterial Endocarditis of Tricuspid Valve. H. L. Goldburgh, S. Barr and M. M. Lieber, Philadelphia.—p. 319.

*Incidence of Acute and Subacute Bacterial Endocarditis in Congenital Heart Disease. R. Gelfman and S. A. Levine, Boston.—p. 324.

Action of Furmethide (Furfuryl-Trimethylammonium Iodide) on Cardiovascular System in Man. P. K. Bondy and M. D. Altschule, Boston.—p. 334.

Mechanism of Arterial Hypertension in Experimental Hydronephrosis. R. S. Megibow, L. N. Katz and S. Rodbard, Chicago.—p. 340.

Effect of Pregnancy on Experimental Renal Hypertension in Rats. P. P. Foà, Naomi L. Foà and M. M. Pret, Ann Arbor, Mich. —p. 350.

Quantitative Urobilinogen Excretion Following Transfusions of Stored and Fresh Blood. L. R. Wasserman, M. Volterra and N. Rosenthal, New York.—p. 356.

Effect of Large Amounts of Single Vitamins of B Group on Rats Deficient in Other Vitamins. K. Unna and Josephine D. Clark, Rahway, N. J.—p. 364.

Studies of Effects of Million Volt Roentgen Rays, 200 Kilovolt Roentgen Rays, Radioactive Phosphorus and Neutron Rays by Marrow Culture Technic. E. E. Osgood, Portland, Ore.; P. C. Aebersold, L. A. Erf, Berkeley, Calif., and Evelyn A. Packham, Portland, Ore. —p. 372.

Pathologic Changes in Brains of Dogs Given Repeated Electrical Shocks. K. T. Neuburger, R. W. Whitehead, Enid K. Rutledge and F. G. Ebaugh, Denver.—p. 381.

Intramuscular Pressure: III. Action of Various Drugs on Patients with Normal Intramuscular and Venous Pressure. L. Gunther, L. Strauss, H. H. Henstell and H. Engelberg, Los Angeles.—p. 387.

Id.: IV. Venopressor Mechanism During Course of Surgical Procedures. L. Gunther, H. H. Henstell, L. Strauss and H. Engelberg, Los Angeles.—p. 394.

Action of Steroid Compounds on Vaginal Epithelium of Rat. Eleanor Clarke and H. Selye, Montreal, Canada.—p. 401.

Treatment of Acute Opium Poisoning: Beneficial Effect of Coramine. I. Snapper, I. K. C. Chu and Teh-Yueh Cheng, Peiping, China. —p. 409.

Micromethod for Determining Prothrombin Time on Fresh Capillary Blood Using Standard Physical Conditions. O. D. Hoffman and R. P. Custer, Philadelphia.—p. 420.

Effect of Propylene Glycol Vapor on Incidence of Respiratory Infections in Convalescent Home for Children: Preliminary Observations. T. N. Harris and J. Stokes Jr., Philadelphia.—p. 430.

*Diagnostic Criteria and Resistance to Therapy in Sprue Syndrome. F. M. Hanes, Durham, N. C.—p. 436.

Apparent Cure of Periarteritis Nodosa with Sulfapyridine: Report of Case. B. A. Goldman, K. L. Dickens and J. R. Schenken, New Orleans.—p. 443.

Acute Bacterial Endocarditis of Tricuspid Valve.—An incidence of 2.5 per cent or 646 cases of acute bacterial endocarditis was found by Goldburgh and his co-workers among 26,007 necropsy records at the Philadelphia General Hospital. In only 20 of these was the tricuspid valve alone involved. If the cases in which the tricuspid and pulmonic valves were affected in association with left sided endocarditis are included, vegetations in the right chambers of the heart were present in 53 cases. The condition in 9 of the 20 was due to the pneumococcus, making it appear that the pneumococcus attacks the tricuspid valve more frequently than other organisms. If the cases of pneumococcic endocarditis are separated from the group as a whole, 9 of 62 cases of pneumococcic endocarditis, or 14.5 per cent, occurred on the tricuspid valve alone, but only 11 of 584 (1.8 per cent of all other cases of acute bacterial endocarditis) were restricted to the tricuspid valve. The findings on auscultation are apparently unreliable, as in only 8 of the 20 was it mentioned that any murmur was heard and in none of these was it heard specifically over the tricuspid area. Vegetations may be large without producing cardiac murmurs. The absence of auscultatory changes should not eliminate a diagnosis of bacterial endocarditis. The continuance of a positive blood culture in pneumonia longer than a week should cause one to suspect acute bacterial endocarditis.

Bacterial Endocarditis in Congenital Heart Disease.—The incidence of acute and subacute bacterial endocarditis and endarteritis in hearts with congenital defects is discussed by Gelfman and Levine as they found it from the collected data of four large hospitals in Boston. Congenital cardiac defects were present in 1.33 per cent or in 453 of 34,023 necropsies, but only 0.5 per cent were of persons more than 2 years of age (181 cases). The incidence of superimposed bacterial endocarditis and endarteritis was 6.6 per cent in the whole group and 16.6 per cent in the group more than 2 years of age. The distribution of males and females was in a proportion of 3 to 2 in both the total group with cardiac defects and in those who showed infectious endocarditis. Sixty per cent of the patients died before the age of 2 years, and for the rest there was no predominance in any one age group. The highest incidence of bacterial endocarditis was in the second and third decades. In 25 of the 181 more than 2 years of age with congenital cardiac defects there was the further complication of rheumatic infection. Congenital bicuspid aortic valve and interauricular septal defects were the most frequent underlying cardiac anomalies, and subacute bacterial endocarditis was present in 8 of the 25. The incidence of bacterial endocarditis for interauricular septal defects for the group was none, for interventricular septal defects 42 per cent, for patent ductus arteriosus 28.6 per cent, for bicuspid valves 17.4 per cent, for the tetralogy of Fallot 12.5 per cent and for pulmonic stenosis 19 per cent. The respective figures for patients more than 2 years of age was also none, 57, 20, 21, 29 and 29.

Therapy in Sprue Syndrome.—Hanes reports 4 cases in which, though the most stringent diagnostic requirements of the sprue syndrome were fulfilled, there was poor or no response to adequate liver and dietary therapy. It is frequently impossible to establish the diagnosis of sprue without a quantitative estimation of the fats in the stool. The differential possibilities to be considered in its diagnosis are pernicious anemia, multiple avitaminoses, pancreatic disease, tabes mesenterica, gastrocolic fistula, anorexia nervosa and Simmonds' disease. The sprue in the 4 cases was decidedly refractory to the usual form of therapy. Under certain conditions the morbid process appears to be irreversible. The reason for such occasional refractoriness is not known. Three of the 4 patients died, and the necropsy of 2 revealed changes similar in every way to those reported by other observers; that is, extreme inanition which was inadequate to explain the fatal outcome.

Annals of Internal Medicine, Lancaster, Pa.

17:407-584 (Sept.) 1942

*Primary Coccidioidomycosis: Roentgenographic Study of Forty Cases. W. A. Winn and G. H. Johnson, Springville, Calif.—p. 407.

Vitamin B Therapy in Paralytic Agitans. Winifred C. Loughlin, H. A. Myersburg and H. Wortis, New York.—p. 423.

Urinary Tract in Diabetic Women: Its Contribution to Incidence of Hypertension. B. D. Bowen and N. Kutzman, Buffalo.—p. 427.

Hypertensinase Content of Plasma of Normal, Hypertensive and Nephrectomized Dogs. L. Dexter, Boston.—p. 447.

Sensitivity to Hypertensin, Adrenalin and Renin of Unanesthetized Normal, Adrenalectomized, Hypophysectomized and Nephrectomized Dogs. B. A. Houssay, Buenos Aires, Argentina, and L. Dexter, Boston.—p. 451.

Destruction and Elimination of Renin in Dog. B. A. Houssay, E. Braun-Menendez, Buenos Aires, Argentina, and L. Dexter, Boston. —p. 461.

*Studies on Etiology and Serum Treatment of Encephalitis During Epidemic in North Dakota and Minnesota (1941). E. C. Rosenow and H. W. Caldwell, Rochester, Minn.—p. 474.

Psychologic Aspects of Heart Disease. E. D. Hoedemaker, Seattle. —p. 486.

Spontaneous Hemopneumothorax: Report of Three Cases and Review of Literature. H. C. Hartzell, Cleveland.—p. 496.

Bacterial Endocarditis and Congenital Heart Disease: Report of Two Cases. A. J. Antenucci and G. F. Eckhardt, New York.—p. 511.

Primary Coccidioidomycosis.—Winn and Johnson observed the roentgen pulmonary features in 40 cases of primary coccidioidomycosis from the clinical illness and until they cleared, remained stable or progressed. Depending on the amount of

infection, a small nodular area of opacity may be all that is visible or, on the other hand, there may be single or confluent areas of pneumonitis in the pulmonary bases. In many instances the lesions appear predominantly exudative and clear rapidly. Occasionally a little residual fibrosis may remain. There is a tendency for pulmonary foci of primary coccidioidal infection to appear like productive lesions and then to clear and decrease in size slowly and incompletely, leaving nodular densities suggesting caseation that eventually may calcify. Calcified pulmonary lesions in children with positive cutaneous reactions to coccidioidin and negative reactions to old tuberculin and to purified protein derivative are evidences of previous coccidioidal infection. The cavity formation that accompanies the early acute phase, usually single, may close spontaneously or it may persist despite regression of the other pulmonary lesions. It then becomes thin walled and cystlike in appearance with little or no surrounding collateral reaction and changes little in size, shape or appearance in several years. Although these cavities serve as reservoirs for the existence and growth of Coccidioides immitis they apparently cause no injury to the health of the person. They are frequently the source of small repeated hemoptysis, which is the only factor leading to their detection. Localized bronchiectasis may also result from coccidioidal infection. Initial infection is sometimes manifested by a primary pleuritic effusion with Coccidioides immitis in the fluid. Secondary mediastinal or hilar adenopathy in primary coccidioidal infection is infrequent but, when visible, has preceded fatal dissemination of the disease. Primary coccidioidomycosis is seldom a progressive disease, but if it is it is acute or chronic in its dissemination. Distribution suggests systemic seeding via the blood stream, with entry from involved lymph nodes. Hence the seriousness of advancing adenopathy following the initial infection. Acute disseminating primary coccidioidomycosis is probably always fatal in five weeks to seven months. Chronic disseminating coccidioidomycosis (coccidioidal granuloma) has a mortality of 50 to 60 per cent. The coming of many uninfected persons, especially military personnel, into inland California valleys and certain parts of Arizona and Texas will result in a proportionate increase in the incidence of coccidioidal infection.

Etiology and Serum Treatment of Encephalitis.—In their study of the etiology of encephalitis as it occurred in the summer and autumn of 1941, Rosenow and Caldwell noticed that the manner of spread and the incidence of the disease were strikingly like those in epidemic poliomyelitis. Definitely a specific encephalitis type of streptococcus was isolated from the nasopharynx, stools, brain and spinal fluid of patients and from the brain of horses and other animals having encephalitis or which had died from it. The streptococcus was agglutinated specifically by human and equine antistreptococcus serums, by the equine encephalomyelitis antiviral serum (western type) and by serum of patients convalescing from encephalitis. The presence of this particular streptococcus among ill persons and animals, and in well "contacts" and "noncontacts" and in outdoor air in the epidemic zone is of great epidemiologic importance suggesting that the disease may be air borne. Only patients for whom a diagnosis could be made definitely by means of spinal puncture or the classic signs and symptoms of the disease received serum treatment. The results are strikingly favorable, especially when treatment was started early in the course of the disease. The effect of serum was most striking in relieving the distressing headache (within a few hours) and nausea and vomiting than the effect on the duration of fever (about six and a half days). At first patients received 10 or 20 cc. of serum intramuscularly once or twice a day. Later, because of the frequent return of cutaneous tests to positive, the dose was 5 cc. at intervals of four hours. A secondary increase in temperature was prevented in this manner. Not infrequently a secondary increase in temperature appeared when serum therapy was stopped, and for this reason the authors recommend that treatment with serum be continued for at least one day after the temperature has returned to normal. An occasional temporary increase in temperature occurred as an immediate reaction. Hives usually developed as a late reaction.

Archives of Dermatology and Syphilology, Chicago

64:337-468 (Sept.) 1942

New Approach to Problem of Disseminated Neurodermatitis. M. F. Engman Jr. and R. C. MacCardle, St. Louis.—p. 337.
Pemphigus: Clinical Analysis and Follow-Up Study of Sixty-Two Patients. W. F. Lever and J. H. Talbott, Boston.—p. 348.
Keratoconus Associated with Atopic Dermatitis: Report of Two Cases. E. S. Bereston, Baltimore, and R. L. Baer, New York.—p. 358.
Disseminated Lupus Erythematosus: Report of Two Cases with Unusual Clinical Manifestations. B. V. Jager, Baltimore.—p. 362.
Symmetric Syphilitic Granulomas of Elbows. J. A. Tuta and R. A. Coombs, Chicago.—p. 373.
Use of Sulfanilamide and Its Derivatives in Ointment Form: Local Treatment of Cutaneous Diseases. J. L. Miller, New York.—p. 379.
*Toxic Eruptions Due to Phenobarbital: Report of Two Cases. R. E. Moss and W. E. Long, Boston.—p. 386.
Granuloma Annulare. F. C. Prunty and H. Montgomery, Rochester, Minn.—p. 394.
Atrophy of Skin and Subcutaneous Fat. L. Hollander and C. L. Schmitt, Pittsburgh.—p. 414.
Epidermolysis Bullosa Hereditaria: Report of Two Cases with Extensive Family Histories. M. Leider and R. L. Baer, New York.—p. 419.
Cutaneous Sensitivity to Merthiolate and Other Mercurial Compounds. F. A. Ellis and H. M. Robinson Jr., Baltimore.—p. 425.
Absorption of Vitamin A Through Human Skin. J. Mandelbaum and L. Schlesinger, Brooklyn.—p. 431.

Toxic Eruptions Due to Phenobarbital.—Two cases of severe toxic eruption following the use of phenobarbital are reported by Moss and Long. Both patients recovered. In addition to the skin, all the mucosal surfaces, except the bronchial and urinary systems, were obviously affected. No loss of hair occurred, but each patient eventually shed all finger and toe nails. One of the patients took 1.53 Gm. of phenobarbital in twenty days and the other 4.8 Gm. in thirty-nine days. The authors suggest that phenobarbital intoxication may well have been the causative agent in many cases recorded in the literature as "atypical erythema exudativum multiforme" of unknown cause. They say that the cutaneous and mucosal eruptions of these cases resembled closely those of their 2 patients.

Archives of Ophthalmology, Chicago

28:385-580 (Sept.) 1942

Uveitis with Poliosis, Vitiligo, Alopecia and Dysacousis (Vogt-Koyanagi Syndrome). H. F. Carrasquillo, Utuado, Puerto Rico.—p. 385.
*Cortical Representation of Macula Lutea, with Special Reference to Theory of Bilateral Representation. T. J. Putnam, New York, and S. Liebman, Boston.—p. 415.
Unusual Disciform Retinal Lesion with Heterotopia Maculae. B. Friedman, New York.—p. 444.
The Cornea: IV. Hydration Properties of Whole Cornea. V. E. Kinsey and D. G. Cogan, Boston.—p. 449.
Cure of Depression of Lower Lid Following Reinsertion of Inferior Rectus Muscle: Report of Case. J. A. Inciardi, Brooklyn.—p. 464.
*Pits or Crater-like Holes in Optic Disk. J. N. Greear Jr., Washington, D. C.—p. 467.
Use of Padgett Dermatome in Ophthalmic Plastic Surgery. B. Smith, New York.—p. 484.
Combination of Cross Cylinder and Astigmatic Chart in Correction of Astigmatism. A. Wilson, Washington, D. C.—p. 490.
Riboflavin: Significance of Its Photodynamic Action and Importance of Its Properties for Visual Act. M. Heiman, Mount Pleasant, Iowa.—p. 493.
Hyaline Scleral Plaques. P. H. Boshoff, Johannesburg, Union of South Africa.—p. 503.
Value of Orthoptic Fusion Training Exercises in Strabismus and Related Conditions. Mary Jane Fowler, Chicago.—p. 507.
Lymphosarcoma of Lacrimal Gland: Report of Case with Giant Lymph Follicle Hyperplasia. C. A. Perera, New York.—p. 522.

Cortical Representation of Macula Lutea.—Putnam and Liebman review the origin and development of the conception of the cortical representation of the macula, especially of bilateral representation of both halves of the macula, and evaluate the available data. The preponderance of evidence favors extremely large representation of central vision at the posterior end and in the depths of the calcarine fissure. Central vision may have some representation even at the anterior end of the fissure and, if it does, it is doubtless in the portion adjacent to the ventricle. There is considerable evidence that a callosal bundle uniting one geniculate body with the striate cortex of the opposite side does not exist. Many cases are recorded in which a homonymous hemimacular scotoma existed, but the lesion in the only brain examined was found at the tip of the occipital lobe. Usually the lesion has been traumatic and presumably injured the optic radiation. Unilateral lesions of the anterior portion of the striate area produce a contralateral hemianopsia with a large remnant of central vision. Lesions of the tip of the occipital pole produce a hemianopsia with irreg-

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ular boundaries, sometimes with only 1 or 2 degrees of central vision. Neither type of central field is actually "macular." Total or subtotal lesions of one occipital lobe may produce either a complete hemianopsia or one with varying traces of central vision. The persistence of central vision when a lesion of the occipital lobe exists may be due to extensive representation of macular vision. Another explanation for a tiny remnant of central vision is that there is a constant physiologic shift of fixation. In some cases a new fixation point is formed within the preserved field. Finally a certain degree of visual perception may be taken over by lower centers after occipital lesions.

Pits in Optic Disk.—Greear reviews 69 cases of congenital deformity, pit or crater-like depression, of the optic disk reported in the literature since 1882, when Wiethe cited the first case, and 3 cases of his own. Central field changes were present in the 3 and also peripheral field changes in 1. These pits or crater-like holes of the disk should be classified as atypical colobomas. In all cases studied pathologically, pigment epithelium has been present in the pit or hole. No further explanation appears necessary for the ophthalmoscopic appearance of the excavation.

Archives of Pathology, Chicago

34:473-612 (Sept.) 1942

*Carcinoma of Prostate: Correlation Between Histologic Observations and Clinical Course. N. Evans, R. W. Barnes and A. F. Brown, Los Angeles.—p. 473.
Coccidioidomycosis in States Other Than California: Report of Case in Louisiana. J. R. Schenken and E. E. Palik, New Orleans.—p. 484.
Metastatic Tumors of Nervous System. A. B. Baker, Minneapolis. —p. 495.
Cultivation of Human Leukemic Leukocytes on Chorioallantoic Membrane of Chicken Egg. Mils Pierce, Chicago.—p. 538.
Multiple Myeloma with Unusual Visceral Involvement: Case Report. J. Churg and A. J. Gordon, New York.—p. 546.
Myocardial Lesions in Myasthenia Gravis: Review and Report of Case. A. Rottino, R. Poppiti, New York, and J. Rao, Detroit.—p. 557.
Effects of Radiation on Normal Tissues: Effects of Radiation on Blood and Hemopoietic Tissues, Including Spleen, Thymus and Lymph Nodes. S. Warren and C. E. Dunlap, Boston.—p. 562.

Carcinoma of Prostate.—Evans and his associates determined the effect the grade of 100 consecutive cases of carcinoma of the prostate, studied between 1925 and 1936 and followed until death or for at least five years, had on life expectancy. Necropsy was done in 25, while 9 patients are still living. Study of the average survival time shows a decided decrease as the malignant grade of the carcinoma increases when grading was based on acinous structure, cell structure and nuclei. The same relationship was noted with the composite grade, so that a survival time of five and four-tenths years in grades 1 and 2 (combined) decreases to two and two-tenths years in grade 4. The percental incidence of metastasis was 20, 29 and 44 in composite grades 1-2, 3 and 4, respectively. The higher grades of carcinoma occurred at slightly earlier ages than the lower. Roentgen therapy appeared to lengthen the survival time, especially of patients with the higher grades of carcinoma.

Archives of Physical Therapy, Chicago

23:513-576 (Sept.) 1942

*Treatment of Neurosyphilis by Artificial Fever Chemotherapy. H. W. Kendell, W. M. Simpson and D. L. Rose, Dayton, Ohio.—p. 517.
Rationale of Oxygen Therapy During Fever Therapy. S. C. Cullen, E. F Weir and Evelyn Cook, Iowa City.—p. 529.
*Ultraviolet Blood Irradiation Therapy. G. Miley, Philadelphia.—p. 536.
Two Point Coagulation: Follow-Up Report on New Technic and Instrument for Electrocoagulation in Neurosurgery. J. Greenwood Jr., Houston, Texas.—p. 552.

Artificial Fever Therapy for Neurosyphilis.—Since 1931 Kendell and his associates have subjected 1,376 neurosyphilitic patients to artificial fever therapy and chemotherapy. During the first six years the usual course of treatment consisted of ten weekly five hour sessions of artificial fever at 105 to 106 F. After the combined fever and chemotherapy was completed the patients received twenty weekly injections of bismuth and arsenic preparations. During the last five years the fever therapy was reduced to twelve three hour sessions, and many patients were treated two and three times a week. These more frequent sessions have proved advantageous, particularly since the advent of hospital insurance, as the patient can be admitted for thirty days and receive a full course of treatment. Only 271 neurosyphilitic patients observed for not less than eighteen months are considered in the report. The records of 64 are excluded because of incomplete post-therapy observation. The records of the remaining 208 show that the remission rate was 52 per cent and that an additional 28 per cent were improved. Thus a total of 80 per cent of the patients were benefited. The successful results are sufficiently comparable to justify the categorical statement that artificial fever therapy is at least as effective as malaria therapy in the management of symptomatic or asymptomatic neurosyphilis. Many reliable investigators have obtained significantly superior results with artificial fever therapy, patients tolerate artificial fever therapy better, the treatment can be carried out on an ambulatory basis without interrupting employment, and complications are minimized. The concurrent use of chemotherapy and artificial fever increases the therapeutic effectiveness of both agencies.

Ultraviolet Blood Irradiation.—Miley injected into 71 patients with peritonitis blood that was irradiated with ultraviolet. Of 39 with generalized peritonitis 32 recovered: 100 per cent of those with moderately advanced peritonitis and 53 per cent of those who were apparently moribund. Signs of early detoxification appeared within an average of thirty-four and five-tenths hours after initial irradiation; the average complete detoxification time was eighty-one and three-fourths hours. Twenty-nine patients received one, 6 two and 4 more than two treatments. Ultraviolet blood irradiation was used to control infection of 20 with localized peritonitis and appendical abscess; 17 recovered: 100 per cent of those with moderately advanced infection and 75 per cent of the apparently moribund. The average early detoxification was apparent in twenty-four and seventy-one hundredths hours and complete detoxification in fifty-two and ninety-four hundredths hours. Fifteen patients had one irradiation, 4 two and 1 more than two. Of the 12 patients with severe pelvic peritonitis accompanied by multiple pelvic abscesses 9 recovered: the 3 in whom the peritonitis was moderately advanced and 67 per cent of those who were moribund. Detoxification was apparent in fifty-four hours; complete detoxification occurred in 10 patients at an average of ninety hours. Five patients received one, 6 two and 1 three irradiations. There were 14 deaths; all occurred among the 33 apparently moribund patients.

Canadian Medical Association Journal, Montreal

47:193-292 (Sept.) 1942

*Tuberculosis in the Canadian Army. W. P. Warner, Toronto.—p. 193.
*Post-Traumatic Headache and Dizziness: Study of Causal Injury. P. O. Lehmann and A. R. Elvidge, Montreal.—p. 197.
*Chronic Chlorosis as Operation Hazard: Analysis of 300 Hysterectomies. W. F. Abbott and J. D. Adamson, Winnipeg, Man.—p. 201.
National Health as Postwar Problem. R. E. Wodehouse, Ottawa, Ont. —p. 204.
Cutaneous Ureterostomy as Means of Relief in Contracted Tuberculous Bladders. W. A. Dakin, Regina, Sask.—p. 207.
Subphrenic Abscess. R. K. Magee, Peterborough, Ont.—p. 213.
Intussusception in Adults. P. G. Rowe, Montreal.—p. 219.
Osteomyelitis of Frontal Bone: Observations on Seventeen Cases. A. A. Campbell, Toronto.—p. 226.
Amputations and After Treatment. H. K. MacDonald, Halifax, N. S. —p. 229.
Study of Results Obtained by Section of Ovarian Vessels and Adjoining Tissue in Relief of Certain Types of Pelvic Pain. W. A. Bigelow, Brandon, Man.—p. 233.
Ether, the All Purpose Anesthetic. D. G. Revell Jr., Winnipeg, Man. —p. 235.
Analysis of Neurosyphilis over Five Year Period. A. McCausland and M. Straker, London, Ont.—p. 240.
St. Michael's Hospital Peroral Endoscopic Clinic: Review of Cases over Two Year Period. G. A. Henry, Toronto.—p. 243.
Granuloma Inguinale and Lymphogranuloma Inguinale. H. S. Root, Montreal.—p. 246.
Primary Carcinoma of Vagina: Report of Three Cases. H. W. Johnston, Toronto.—p. 252.
Bronchial Asthma Due to Sensitivity to Acacia. P. H. Sprague, Edmonton, Alta.—p. 253.

Tuberculosis in the Canadian Army.—A survey by Warner shows that 3,987 men, or 1 per cent, were rejected at the time of enlistment for pulmonary tuberculosis and of tuberculosis developing in the Canadian army from September 1939 until March 1942. These men had considered themselves physically fit to join the army. The extent and character of the disease in these men was pleurisy in 73, minimal tuberculosis in 1,970, moderately advanced disease in 1,298, far advanced in 262, 179 with calcified lesions and 196 with supposed tuberculosis. Those with minimal, moderately advanced and far advanced disease had active or potentially active tuberculosis. Only 270 of the minimal cases could be diagnosed on clinical

findings when the lesion had been shown on the roentgenogram. Of the moderately advanced cases 357 could be diagnosed clinically and of the far advanced cases 117. In the series 293 presented a cavity and were obviously open cases. In 48 the tuberculosis could not have been diagnosed or suspected by clinical means. Only 114 men were returned from overseas with clinical tuberculosis which developed in the army from September 1939 to March 1942. The physical status of 10 of them at the time of admission was not up to par and they were enlisted by error. Ninety-six of the 104 were admitted with negative roentgenograms and clinical examination, while 8 showed small apparently healed lesions on admission but were considered fit for service. The 8 must represent a small percentage of those enlisted with small healed lesions. The policy of enlisting such men appears sound and will be continued. The average duration of symptoms in the 104 until the diagnosis of pulmonary tuberculosis was two and seven-tenths months.

Post-Traumatic Headache and Dizziness.—The treatment in 92 consecutive cases of post-traumatic headache and dizziness was assessed by Lehmann and Elvidge to determine, if possible, what factors were responsible for their development. The cases represent one hundred accidents; 2 patients were hurt on three different occasions and 4 on two occasions. The patients, and when necessary the attending physician and the hospital in which treatment was received, were questioned by letter concerning the original treatment received. The 92 patients were admitted to the Montreal Neurological Institute for post-traumatic headache between 1934 and 1940 inclusive. Investigation revealed that 18 had suffered linear fractures of the vault, 2 fractures of the base and 8 minor depressed fractures; in 73 the injury produced no evidence of fracture. There was an immediate loss of consciousness or lapse of memory at the time of the initial injury only after sixty-five of the one hundred injuries. Only 6 had evidence of a cerebral contusion with blood in the cerebrospinal fluid or seizures following the injury. As none of the patients had leaks of cerebrospinal fluid, this may simply be further evidence of the moderate nature of the injuries or, conversely, a leak of spinal fluid in severe injuries may tend to prevent or to minimize post-traumatic headache. Its effect may be similar to that of lumbar puncture: the production of a natural decompression. That this happens is frequently obvious in clinical experience. The headaches were of two types: a dull, heavy, pulsating ache, a sense of pressure, fulness or tightness of the head, which may or may not be throbbing in character but is interpreted by the patient as deep seated, and a sharp, shooting, stabbing, sticking, lancinating, focal pain, usually felt at the site of injury with some radiation. The first type occasionally and the second type frequently is accentuated or influenced by change of posture of the head or head movements. Both types are usually accentuated by excitement, fatigue, mental effort, exertion, changes in the weather and occasionally imbibition of alcohol. The majority of headaches fell into the second group, but many were of both types. Sixty-nine patients complained of dizziness usually induced by stooping and generally independent of headache. Of the 70 patients on whom accurate follow-up data were obtained only 9 had had a lumbar puncture within three days of the accident, while 61 had had none at all. Only 31 were treated in a hospital, while only 47 had had adequate bed rest for their particular injury, 11 had had less than seven to ten days of complete bed rest and 18 had had no bed rest. The few patients who had lumbar puncture were among those who had had adequate bed rest. Fifty-eight of the 92 patients received spinal insufflation of air or air injected under pressure into the subdural space through a trepanation at the site of maximal pain; 28 were definitely improved, 9 moderately improved, 7 unimproved and 14 were said to be improved at the time of discharge but no further follow-up information is available. It is the authors' conclusion that usually patients who come with post-traumatic headache have been poorly treated from the start.

Chronic Chlorosis as Operation Hazard.—To obtain an analysis of the surgical risk, complications encountered and the treatment necessary to improve the results in "chlorotic" patients, Abbott and Adamson studied one major more or less standardized surgical procedure. The treatment of 300 cases for uterine fibroids, so often associated with menorrhagia and secondary anemia and requiring some form of hysterectomy, was chosen for investigation. In 244 the hemoglobin estimation was 65 per cent or more on admission and in 56 it was below this and had to be corrected before operation. A total hysterectomy was performed in 67 and subtotal in 233. The complications were so nearly identical in the two groups that no significance was primarily attached to the type of operation performed. The death rate for total hysterectomy was 2.98 per cent and for subtotal 1.71 per cent. One half of the deaths occurred among the 25 with chronic chlorosis. Infection of the wound was five times as frequent when the hemoglobin was low and six times more frequent in the chronic chlorotic group. Ileus occurred three and one-half times more often in the total anemic group and five and one-half times more often in chronic chlorotic cases. Phlebitis was twenty-five times more common in the chlorotic group; a low hemoglobin is considered to be the main contributory factor. Pulmonary complications showed a similar alarming incidence. The sum total of all complications showed an incidence of 17.5 per cent of postoperative lesions per hundred operations among those with a normal hemoglobin content, 90.7 in the total anemic group and 136 in the patients with chronic chlorosis. When a definite diagnosis of chronic chlorotic anemia is established, the only satisfactory form of therapy is massive doses of iron.

Canadian Public Health Journal, Toronto

33:365-426 (Aug.) 1942

Poliomyelitis: Control and Treatment. D. W. Gudakunst, New York. —p. 365.
Gonorrhea: Preventable Disease. J. A. Leroux, Vancouver, B. C. —p. 374.
Western Equine Encephalitis. G. D. W. Cameron, Ottawa, Ont. —p. 383.
Encephalomyelitis in Saskatchewan, 1941: Preliminary Report. R. O. Davison, Regina, Sask.—p. 388.
Printed Material in Health Education: Its Status in Present Emergency. N. L. Burnette, Ottawa, Ont.—p. 399.

Hawaii Medical Journal, Honolulu

1:347-412 (July) 1942

Random Notes of a Sanatorium Physician. D. R. Chisholm, Kealia, Kauai.—p. 353.
Menière's Disease: Review of Its Diagnostic Features and Report of Four Cases. T. Hata, Kapaa, Kauai.—p. 358.
Loeffler Syndrome: Report of Case. L. C. Beck, Koloa, Kauai.—p. 361.
Massive Dose Arsenotherapy of Early Syphilis: Adapted to Plantation Use; Report of Nine Cases. S. R. Wallis, Lihue, Kauai.—p. 363.
Diphtheria Problem in Waimea District. K. M. Amlin, Waimea, Kauai. —p. 367.
Regional Anesthesia: Experiences in Ten Years of General Practice. M. A. Brennecke, Eleele, Kauai.—p. 369.

Illinois Medical Journal, Chicago

82:177-240 (Sept.) 1942

Macrocytic Anemia. C. J. Watson, Minneapolis.—p. 195.
Use of Anterior Pituitary Extract in Treatment of Allergy. C. S. Bucher, Champaign.—p. 202.
Problems in Treatment of Diabetes Insipidus. A. T. Johnson, Rockford.—p. 205.
Cancer—Deficiency Disease? H. Macdonald, Evanston.—p. 210.
Technic of Suggestion in Therapy of Abnormal Mental States with Some Experimental Data. D. M. Olkon, Chicago.—p. 215.
Concepts of Coronary Disease. J. B. Carter, Chicago.—p. 219.
Mycosis Fungoides: Report of Case with Autopsy Findings. S. J. Zakon and A. P. Falkenstein, Chicago.—p. 224.

Indiana State Medical Assn. Journal, Indianapolis

35:451-548 (Sept.) 1942

Delirium Tremens. D. A. Boyd Jr. and W. B. Rossman, Indianapolis. —p. 453.
Cardiology in General Practice. G. M. Cook, Hammond.—p. 457.
*Chronic Brucellosis. N. Davis, Lowell.—p. 459.
Determination of Alinement in Hip Nailing Procedure. W. D. Davidson, Evansville.—p. 461.
Diagnosis and Treatment of Cardiac Emergencies. R. E. Lyons Jr., Bloomington.—p. 463.
Pregnancy Complicated by Preeclamptic Toxemia and Pernicious Anemia. G. Procopio and C. Armington, Anderson.—p. 466.

Chronic Brucellosis.—Davis believes that the chronic form of undulant fever is prevalent among the rural population, but as its recognition is more difficult it for the most part is overlooked. It is estimated that 10 per cent of the rural population is infected. The two common symptoms shown in all cases are weakness and pain. The patient gets up tired and feels as if the morning will never end. By noon he gains strength and by

evening he feels pretty good. The weakness is usually referred to the hips and knees. Spells of sleepiness may accompany the weakness as in epilepsy, which must be ruled out. Neurasthenia is the usual diagnosis given this phase of brucellosis. The pain, which is common to all cases, may affect any member of the body. It may be a headache or a backache. It may have the subjective symptoms of a herpes zoster without a cutaneous manifestation. In the extremities it may be very excruciating and appear to be a neuritis. At times the pain localizes about a joint and arthritis is thought of. Pain in the chest has had little mention in the literature, but in the author's experience it has been one of the most common and persistent symptoms. It is usually described as precordial; the history usually suggests angina pectoris. However, many differences are present: a low blood pressure, the youth of most of the patients, absence of arteriosclerosis and orthopnea. A paroxysmal tachycardia with a pulse rate as high as 160 per minute may develop at any time. The tachycardia is not always accompanied by an increase in chest pain. Large doses of sedatives are required to produce sleep. The symptoms do not respond to digitalis, aminophylline or the circulatory dilators. Two other conditions that accompany many cases are pelvic disorders and colitis, usually associated with constipation and mucus in the stools. Davis believes that the final diagnosis of chronic undulant fever should be made from clinical observation and confirmed by a therapeutic trial of vaccine rather than by laboratory tests. The vaccine must never be given subcutaneously, as cold abscesses often result. It should be given intramuscularly and, if induration appears at the site of injection, treatment should be suspended until absorption takes place.

Iowa State Medical Society Journal, Des Moines

32:401-444 (Sept.) 1942

Choice of Treatment for Duodenal Ulcer. J. T. Priestley, Rochester, Minn.—p. 401.
Diseases of Pancreas: Review. E. M. Kersten, Fort Dodge.—p. 407.
*Hypothyroidism and Heart Disease. C. W. Smith, Dubuque.—p. 410.
Pediatrics: Past and Present. M. D. Ott, Davenport.—p. 419.
Retinitis Pigmentosa. J. H. McNamee, Des Moines.—p. 421.

Hypothyroidism and Heart Disease.—In discussing the relationship of hypothyroidism to heart disease Smith points out that the myxedematous state speeds up the development of coronary and general arteriosclerosis. Thyroid should be used with caution in any case of myxedema as it may cause rapid relief or aggravate decompensation or heart pain. It has apparently precipitated death in at least 11 reported cases. The onset or aggravation of decompensation or angina should serve as a warning to reduce or discontinue thyroid medication. This dual potential effect of thyroid in myxedema should be borne in mind. It may accomplish much for the heart by clearing up the reversible harmful effects of myxedema or it may precipitate decompensation, pain or infarction by increasing the work required of a heart handicapped by coronary sclerosis. If heart failure in myxedema does not respond to the usual measures, it may to cautiously administered thyroid. Thyroid medication can retard arteriosclerotic degeneration in patients with myxedema. It may also delay arteriosclerosis in patients with less severe degrees of hypothyroidism.

Journal Industrial Hygiene & Toxicology, Baltimore

24:163-212 (Sept.) 1942

Analysis of Industrial Morale. E. D. Chapple, Boston.—p. 163.
*Effects of Daily Exposures to Arc Welding Fumes and Gases on Normal and Tuberculous Animals. L. U. Gardner and D. S. McCrum, Saranac Lake, N. Y.—p. 173.
Industrial Exposure to Tellurium: Atmospheric Studies and Clinical Examination. H. H. Steinberg, Chicago; S. C. Massari, A. C. Miner and R. Rink.—p. 183.
Effect of Irritant Gases on Rate of Ciliary Activity. L. V. Cralley, Iowa City.—p. 193.
Absorption and Excretion of Fluorides: I. Normal Fluoride Balance. W. Machle, E. W. Scott and E. J. Largent, Cincinnati.—p. 199.
Effect of Pervitin (Desoxyephedrine) on Fatigue of Central Nervous System. E. Simonson and N. Enzer, Milwaukee.—p. 205.

Arc Welding Fumes and Gases.—To determine whether the susceptibility of animals to tuberculosis is influenced by the fumes and gases of arc welding, Gardner and McCrum infected guinea pigs with the attenuated strain of tubercle bacillus, strain R_1, by inhalation and then exposed them to concentrations of welding fumes and gases two to three times a day for one year. Generally, repeated exposures to ordinary concentrations did not increase the natural susceptibility and did not reactivate preexisting partially healed pulmonary tubercles to produce progressive tuberculosis. These data are valid for man as well as guinea pigs, as the effects of this irritant were identical with those observed with dusts of marble, soft coal, gypsum and iron ore. Prolonged exposure did not result in any unusual amount of tuberculosis. However, guinea pigs were more susceptible than white mice and white rats. Chemical pneumonia developed in 50 per cent of the exposed guinea pigs and proved fatal in about half of them. In spite of this severe irritation there was no significant effect on the associated primary infection with the attenuated tubercle bacilli. Tubercles developing during exposure were larger, more numerous and localized in different parts of the lung than in unexposed controls. However, they healed at the same rate as those in the controls and never manifested the slightest tendency to become progressive.

Journal-Lancet, Minneapolis

62:317-354 (Sept.) 1942

Blood Pressure as Factor in Mortality. K. W. Anderson, Minneapolis.—p. 341.

Journal of Nervous and Mental Disease, New York

96:245-368 (Sept.) 1942

Treatment of Patients with Epilepsy with Sodium Diphenyl Hydantoinate (Phenytoin Sodium, Dilantin Sodium) and Phenobarbital Combined. H. H. Merritt and C. Brenner, Boston.—p. 245.
Visual Hallucination During Paraldehyde Addiction. M. Heiman, St. Joseph, Mo.—p. 251.
Principle of Primary and Associated Disturbances of Higher Cortical Functions as Applied to Temporal Lobe Lesions. H. A. Teitelbaum, Baltimore.—p. 261.
"Discharging Function" of Convulsive Seizure: Regarding Psychodynamic Mechanism of Healing Process of Artificial Fits by Electroshock. J. Fleischer, Rome, Italy.—p. 274.
Use of d-l, Alpha Tocopherol Acetate (Synthetic Vitamin E) in Various Neuromuscular Disturbances. G. A. Schwarz, G. D. Gammon and R. L. Masland, Philadelphia.—p. 286.
Principle of Integration: Its History and Its Nature. W. Riese, Richmond, Va.—p. 296.

Journal Neuropath. and Exper. Neurology, Baltimore

1:241-350 (July) 1942

Systemic Vascular and Respiratory Effects of Experimentally Induced Alterations in Intraventricular Pressure. R. Meyers, Brooklyn.—p. 241.
Vascular Supply of Hypothalamus in Man. J. M. Foley, T. D. Kinney and L. Alexander, Durham, N. C.—p. 265.
Myoclonus Epilepsy: Clinicopathologic Report of Case. L. Roizin and A. Ferraro, New York.—p. 297.
Gliomatous Tumors in Nasal Region. E. W. Davis, Chicago.—p. 312.
Functional Organization of Sensory Cortex of Cat: II. H. W. Garol, San Francisco.—p. 320.
Experimental Study of Effects Produced by Large Doses of Vitamin B₁. W. Antopol, Newark, N. J., and I. M. Tarlov, Brooklyn.—p. 330.
Histogenesis of Meningiomas, with Particular Reference to Origin of "Meningothelial" Variety. C. B. Courville and K. H. Abbott, Los Angeles.—p. 337.
Experimental Lesions of Pyramidal Tracts in Primates, Accompanied by New Reflex. V. E. Gonda, Chicago.—p. 344.
Rapid Method for Differentiation of Nerve Cells in Old Formalin Fixed Material. Meta A. Neumann, Washington, D. C.—p. 348.

Journal of Neurophysiology, Springfield, Ill.

5:325-414 (Sept.) 1942

Changes in Normal Electroencephalogram of Macaca Mulatta with Growth. Margaret A. Kennard and L. F. Nims, New Haven, Conn.—p. 325.
Effect on Electroencephalogram of Lesions of Cerebral Cortex and Basal Ganglionic in Macaca Mulatta. Margaret A. Kennard and L. F. Nims, New Haven, Conn.—p. 335.
Modification of Cortical Activity by Means of Intermittent Photic Stimulation in Monkey. W. C. Halstead, G. W. Knox and A. E. Walker, Chicago.—p. 349.
Relation of Fibrillation to Acetylcholine and Potassium Sensitivity in Denervated Skeletal Muscle. J. W. Magladery and D. Y. Solandt, Toronto, Canada.—p. 357.
Cerebellar Action Potentials in Response to Stimulation of Proprioceptors and Exteroceptors in Rat. R. S. Dow and R. Anderson, Portland, Ore.—p. 363.
Comparison of Effects of Upper and Lower Motor Neuron Lesions on Skeletal Muscle. D. Y. Solandt and J. W. Magladery, Toronto, Canada.—p. 373.
Stimulus Frequency as Means of Analyzing Synaptic Activity. C. G. Bernhard and R. Granit, Stockholm, Sweden.—p. 381.
Central Excitatory State Associated with Postural Abnormalities. J. S. Denslow and C. C. Hassett, Kirksville, Mo.—p. 393.
Function of Components of Respiratory Complex. R. F. Pitts, New York.—p. 403.

Journal of Nutrition, Philadelphia

24:199-306 (Sept.) 1942

Absorption and Retention of Carotene and Vitamin A by Hens on Normal and Low Fat Rations. W. C. Russell, M. W. Taylor, H. A. Walker and L. J. Polskin, New Brunswick, N. J.—p. 199.
Effectiveness of Linoleic, Arachidonic and Linolenic Acids in Reproduction and Lactation. F. W. Quackenbush, F. A. Kummerow and H. Steenbock, Madison, Wis.—p. 213.
Linoleic Acid, Pyridoxine and Pantothenic Acid in Rat Dermatitis. F. W. Quackenbush, H. Steenbock, F. A. Kummerow and B. R. Platz, Madison, Wis.—p. 225.
Nicotinic Acid in Foods. R. W. McVicar and G. H. Berryman, Washington, D. C.—p. 235.
Salt Mixture for Use with Basal Diets Either Low or High in Phosphorus. J. H. Jones and Claire Foster, Philadelphia.—p. 245.
Sulfur Metabolism of Children. E. F. Beach, D. M. Teague, Olive D. Hoffman, Bertha Munks, Frances C. Hummel, H. H. Williams and Icie G. Macy, Detroit.—p. 257.
Effect of Pantothenic Acid Deficiency on Blood Lipids of Dog. J. V. Scudi and Margaret Hamlin, Rahway, N. J.—p. 273.
Interrelationship of Calcium, Phosphorus and Nitrogen in Metabolism of Preschool Children. Jean E. Hawks, Merle M. Bray, Marjorie Olson Wilde and Marie Dye, with assistance of Veda Hiller Wiltgen and Anne Kilpatrick, East Lansing, Mich.—p. 283.
Effect of Level of Protein Intake on Urinary Excretion of Riboflavin and Nicotinic Acid in Dogs and Rats. H. P. Sarett, J. R. Klein and W. A. Perlzweig, Durham, N. C.—p. 295.

Journal of Pediatrics, St. Louis

21:289-434 (Sept.) 1942

*Notes Concerning Cause and Treatment of Celiac Disease. C. D. May, J. F. McCreary and K. D. Blackfan, Boston.—p. 289.
Posture Habits in Infancy Affecting Foot and Leg Alinements. H. E. Thelander and Mabel L. Fitzhugh, San Francisco.—p. 306.
*Sulfathiazole in Treatment of Measles and Its Complications. H. Gibel and A. M. Litvak, Brooklyn.—p. 315.
Relative In Vitro Effects of Sulfonamides on Hemophilus Influenzae. M. Novak and Anna Margaret Lacy, Chicago.—p. 321.
Subcutaneous Administration of Sodium Sulfadiazine. G. M. Jorgensen and D. M. Greeley, New York.—p. 325.
*Antagonism of Pitressin and Adrenal Cortical Extract in Human Diabetes Insipidus. J. A. Anderson and W. R. Murlin, Minneapolis.—p. 326.
Use of Age at First Appearance of Three Ossification Centers in Determining Skeletal Status of Children. Clara C. Buehl and S. I. Pyle, Cleveland.—p. 335.
Outbreak of Acute Conjunctivitis of Unknown Etiology. J. H. Landes, Brooklyn.—p. 343.
Pertussis Prophylaxis: Clinical Study. J. F. Coppolino, Philadelphia.—p. 348.
Early Treatment of Poliomyelitis. J. A. Toomey, Cleveland.—p. 353.
Ascending Myelitis Complicating Measles. J. O. Rydeen, Norfolk, Va., and J. Glaser, Rochester, N. Y.—p. 374.
Acute Phosphorus Poisoning: Report of Case with Recovery. M. A. Brescia and J. M. DeSabina, Queens, N. Y.—p. 378.
Nephrocalcinosis: Case Report. H. Wohl, New York.—p. 382.
Don't Take Your Word for It. Jean V. Cooke, St. Louis—p. 386.
Food Contaminations and Poisons: Part I. G. M. Lyon, Huntington, W. Va.—p. 392.

Celiac Disease.—The data from a study of 40 patients with celiac disease treated by May and his associates during the last four years with a combination of crude extracts of liver and the B complex of vitamins show that benefit was irregular and usually only partial when any one of the substances was used alone. But definite improvement in the absorption of vitamin A and the clinical condition was invariably obtained in a relatively short time when both extracts were given intramuscularly in large amounts. The authors have no evidence as to the means by which absorption from the intestine in celiac disease is improved by the two extracts. One obvious hypothesis is that some defect in the phosphorylation process in the mucosa is the cause of the impaired absorption. On this premise some factor or factors in the crude extracts might be considered to play an indispensable role in phosphorylation. The treatment consists in 2 cc. of liver extract injected intramuscularly into the buttocks one day and 4 cc. of the B complex the next day in the alternate buttock. If induration occurs and persists, a day of rest is given. The injections should be continued for three weeks or until definite clinical improvement is observed. After this vitamin B complex should be given orally, at least 1 teaspoon four times a day until all the features of the celiac disease have disappeared. If improvement is not maintained by oral therapy, another series of parenteral injections is indicated. Most patients were given a normal diet from the very outset of treatment. The usual supplement of vitamins A, D and C should be given, preferably in amounts twice the accepted daily requirements.

Sulfathiazole in Treatment of Measles.—The value of sulfathiazole in the treatment of measles and the prevention of its complicating infections caused by streptococci, pneumococci and staphylococci was studied by Gibel and Litvak at the Kingston Avenue Hospital during the measles epidemic of December 1940 to June 1941. It was the most extensive epidemic of measles that greater New York has ever experienced; 79,637 cases were reported to the health department between January and June 1941. During this epidemic 1,213 cases were treated at the Kingston Avenue Hospital. All patients less than 6 admitted to the measles service were divided into two groups: one group was treated with sulfathiazole and the other group was treated symptomatically. The only exception to this was that all patients admitted with bronchopneumonia were treated with sulfathiazole. There were 201 cases in the control group and 200 in the sulfathiazole group. The course of the disease itself was not influenced. The common secondary complications (catarrh, bronchitis or purulent otitis media) did not respond to chemotherapy, while bronchopneumonia responded promptly, although bronchopneumonia developed in 6 previously uncomplicated cases during chemotherapy. The period of hospitalization was not reduced by using sulfathiazole. There was only one death among the 47 patients whose measles was complicated by bronchopneumonia.

Pitressin and Adrenal Cortex Extract in Diabetes Insipidus.—Anderson and Murlin undertook studies to determine whether or not the already existing polyuria of diabetes insipidus of undetermined etiology in a boy of 9 would be aggravated by adrenal cortex extract. The study has confirmed the physiologic antagonistic action of adrenal cortex extract and pitressin on the excretion of sodium, chloride and water in the human subject with diabetes insipidus. Adrenal cortex extract did not increase the excretion of potassium unless pitressin was supplied. The suggestion is offered that facultative reabsorption of water as induced by pitressin must be in progress before the kidney tubule can selectively excrete sodium and potassium ions.

Kansas Medical Society Journal, Topeka

43:325-368 (Aug.) 1942

Treatment of Duodenal Ulcer. C. W. Mayo, Rochester, Minn.—p. 325.
Elastic Adhesive Bandage on Burn of Foot. M. A. Walker, Kansas City.—p. 329.
Hodgkin's Disease Complicated by Brucellosis. M. Bernreiter, Kansas City.—p. 330.
The Family Physician and Psychoneuroses. F. A. Carmichael, St. Joseph, Mo.—p. 333.
Cancer of Ampulla of Vater. H. S. Blake and W. M. Mills, Topeka.—p. 335.
Acute Intestinal Obstruction. S. S. Ellis, Coffeyville.—p. 338.
Tests to Determine Alcoholic Intoxication. W. H. McKean, Kansas City.—p. 343.
*Prefrontal Lobotomy in Certain Abnormal Mental States. R. L. Drake and J. S. Hibbard, Wichita.—p. 345.
Insulin Treatment in Chorea. A. C. Eitzen, Hillsboro.—p. 347.

Prefrontal Lobotomy in Certain Abnormal Mental States.—The results following prefrontal lobotomy in approximately 500 cases of certain mental disorders in this country and abroad indicate that the most suitable patient is one who is suffering from a persistent and intense degree of anxiety or apprehension. However, as anxiety may be present in almost any of the abnormal states, Drake and Hibbard find that the best response has followed in anxiety states, obsessive-compulsion reactions, agitated depressions and agitated schizophrenia. The results have not been so good in chronic encephalitis, chronic alcoholism and chronic schizophrenia. The more intelligent the patient, the better is the response. In considering the operation the degree of anxiety versus the possible postoperative defects and sequelae must be weighed. A most important feature is the fact that the intelligence is generally unaffected. There is often an apparent inability to foresee accurately the results of a series of planned acts as they relate to the individual himself. He becomes satisfied with something less than perfection. Memory for recent events shows transitory disturbance but for remote events it remains intact. Complete relief of symptoms in a case of anxiety neurosis following prefrontal lobotomy is reported by the authors. The operation should be performed only on those patients who have proved refractory to other forms of therapy and whose outlook is poor for ultimate recovery.

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Kentucky Medical Journal, Bowling Green

40:339-392 (Sept.) 1942

Subacute Bacterial Endocarditis. L. T. Minish Jr., Louisville.—p. 381.
Renal Complications Following Use of Sulfathiazole. A. J. Miller, H. L. Clay and A. B. Ortner, Louisville.—p. 383.
Myocarditis and Myocardosis from Standpoint of General Practitioner. C. E. Gaupin, Louisville.—p. 386.

Michigan State Medical Society Journal, Muskegon

41:709-812 (Sept.) 1942

Factors in Deficiency Disease. V. P. Sydenstricker, Augusta, Ga.—p. 737.
B Vitamins in Dermatology, with Special Study of Vitamin B₆ (Pyridoxine). C. S. Wright, Philadelphia.—p. 744.
Clinical Use of Diuretics. R. H. Lyons, Ann Arbor, and S. D. Jacobson, Eloise.—p. 749.
*Differential Diagnosis of Benign and Malignant Ulcerating Gastric Lesions. H. M. Pollard and W. C. Scott, Ann Arbor.—p. 754.

Ulcerating Gastric Lesions.—According to Pollard and Scott, the differentiation of benign from malignant ulcers of the stomach requires the full cooperation of the patient, the clinician, the laboratory, the roentgenologist and the gastroscopist. Helpful inferences may be had from the history, but no absolute opinion is possible. A physicial examination is not always helpful. A gastric analysis gives absolute aid in that an ulcerating lesion with persistent achlorhydria must be regarded as malignant. The original roentgen study, while of great importance, does not always establish the diagnosis accurately. Gastroscopy is frequently a valuable adjunct, but it is not infallible. A careful follow-up examination, after a carefully supervised period of medical treatment, is of the greatest importance. Persistent occult blood in the stool should suggest a malignant status. Anything but complete relief from symptoms is of no value as a differential point, and this may occur in carcinoma. Complete healing as depicted in the roentgenogram is highly suggestive of a benign lesion but can also occur in a malignant one. The only safety lies in thorough investigation at every stage of the diagnostic procedure and in following the patient to complete sustained healing when the final diagnosis of benign gastric ulcer implies that there no longer is an ulcer.

Military Surgeon, Washington, D. C.

91:257-378 (Sept.) 1942

Plan for Care of Surgical Casualties in the Armored Division. H. C. Eddy.—p. 257.
The Doctor in War. L. A. Fox.—p. 283.
Pilonidal Cyst and New Improved Type Operation. C. J. DePrizio.—p. 292.
Treatment of Burns. E. C. Gay.—p. 298.
Destruction of Housefly Larvae and Pupae in Sewage Sludge Beds. H. Spencer, L. Hedden and L. B. Dworsky.—p. 306.
Pittressin Hydration Test in Diagnosis of Idiopathic Epilepsy. D. W. Hilger, A. R. Mueller and A. E. Freed.—p. 309.
Keeping Men with Psychiatric Records Out of the Army. A. R. Koontz.—p. 313.
Malingering in Military Ophthalmology. H. S. Sugar.—p. 314.
Ununited Fractures of Symphysis of Mandible. H. L. Hubinger.—p. 320.
Use of Cartilage Transplants in Reconstruction of Facial Architecture. D. Pelliciari.—p. 324.
*Black Widow Spider Bite Syndrome. L. Frank.—p. 329.
Abscess of Tongue. W. H. Gerwig Jr. and A. Dick.—p. 337.
Tuberculoid Leprosy: Report of Case in Soldier. C. S. Livingood, T. E. Patton and A. O. Hecker.—p. 341.
*Fatal Coronary Occlusion in Apparently Normal Soldier. J. A. Sterling.—p. 343.
Trichophytin Foot Infections: Empiric Study of Camphor-Phenol Treatment. S. D. Strauss.—p. 348.
The First Flight Surgeon. R. J. Hunter.—p. 349.

Black Widow Spider Bite Syndrome.—A heretofore undescribed sign of arachnidism, a burning and stinging sensation of the soles of the feet twenty-four hours after the bite, was observed by Frank in 12 cases encountered during the fall maneuvers with the First Army in the Carolinas. Other than this new sign the syndrome was typical. He suggests using a mosquito bar or netting as an effective control measure. Spraying with crude oil or a mixture of crude oil and creosote will kill the spider. Powdered unslaked lime and kerosene will kill the adult spider in thirty seconds. All webs should be thoroughly sprayed. Such places as open latrines should be suspected and thoroughly coated. The spider is very dangerous after spraying, when it becomes agitated. Personal experience among the officer group in the author's regiment who used mosquito netting revealed the protection afforded: it was not uncommon to see one or even two black widow spiders crawling on the mosquito netting in the morning.

Fatal Coronary Occlusion in Apparently Normal Soldier.—Sterling discusses the death from coronary thrombosis of an apparently physically normal soldier of 25 who suddenly died during a three day motor march unattended by great physical strain. At necropsy the arteriosclerotic changes were similar to those found in much older persons. The soldier was seen at the regimental dispensary in the bivouac area on the second evening of the march. He complained of general weakness and abdominal pain of several days' duration. Examination revealed nothing abnormal, and after a few hours of rest the patient returned for reexamination, at which time a definite bradycardia of 60 per minute, a soft presystolic apical murmur and a transient arrhythmia were present. Epigastric pain, which was not increased by mild exercise, was also present. The patient was given a sedative, was restless during the night, had nausea and desired to defecate. At 2:30 a. m. he was feeling better; at 3 a. m. he had struck his shelter tent with the other men and was rolling his pack, when he suffered an acute attack of dyspnea and pain and became convulsive and moribund. All available measures were ineffective, and he died at 4 a. m. At necropsy severe infarction of the left ventricle and interventricular septum with severe arteriosclerosis of the lower abdominal aorta and of the coronary arteries were present.

Minnesota Medicine, St. Paul

25:681-760 (Sept.) 1942

Recent Trends in Cancer Research. H. B. Andervont, Bethesda, Md.—p. 697.
Evolution of Medical Practice. W. H. Valentine, Tracy.—p. 703.
Prognosis in Heart Disease: Contributions of Electrocardiogram. J. F. Borg, St. Paul.—p. 709.
Ectopic Pregnancy: Analysis of 102 Consecutive Cases. W. P. Sadler, Minneapolis.—p. 714.
Fate of the Major Surgical Case in the Small Hospital. D. P. Anderson Jr., Austin.—p. 720.
Anesthesia in the Small Hospital. H. B. Neel, Albert Lea.—p. 723.
Rural Nursing Problems. Louise Newcombe, Duluth.—p. 727.

Nebraska State Medical Journal, Lincoln

27:301-332 (Sept.) 1942

Ureteral Calculi: Review of 350 Cases. C. C. Higgins, Cleveland.—p. 301.
Sulfadiazine. L. T. Hall, Omaha.—p. 309.
Borderline Hyperthyroidism, or Is It Just Nervousness? H. H. Davis, Omaha.—p. 311.
Clinical Evaluation of Vitamin K in Obstetrics. E. C. Sage, Omaha.—p. 314.
Present Status of Fever Therapy in Neurosyphilis. A. E. Bennett, Omaha.—p. 317.
Carbuncle of Kidney: Report of Case. R. L. Egan and J. M. Thomas, Omaha.—p. 321.
Public Health Education in Nebraska. Nina B. Lamkin.—p. 322.

New England Journal of Medicine, Boston

227:325-362 (Aug. 27) 1942

*Erythema Nodosum. M. H. Poppel and A. M. Melamed, New York.—p. 325.
Practical Outline for Treatment of Burns. D. W. MacCollum, Boston.—p. 331.
*Mebaral in Treatment of Epilepsy. B. Cohen, North Grafton, Mass., and A. Myerson, Boston.—p. 336.
Hypochromic Anemia with Koilonychia (Spoon Nails): Report of Case. B. G. Clarke, Boston.—p. 338.
Virus Pneumonias: I. Pneumonias Associated with Known Nonbacterial Agents; Influenza, Psittacosis and Q Fever. M. Finland and J. H. Dingle, Boston.—p. 342.

Erythema Nodosum.—Poppel and Melamed say that, during the years 1928-1941, 88 patients were discharged from the Mount Sinai Hospital, New York City, with a diagnosis of erythema nodosum. These cases were reviewed from two standpoints: to analyze the clinical data from the point of view of associated diseases and to determine whether any specificity to the mediastinal or hilar adenopathy, or both, is shown roentgenologically. The survey indicates that the condition may be found during the course of various diseases, both infectious and noninfectious, virus, bacterial, chemical and toxic. It is evident that no common agent causes these diseases. In a small group of patients (approximately 15 per cent) no evident associated disease was present. Associated with the erythema nodosum were tuberculosis (4 cases), rheumatic heart disease (7 definite and 10 questionable cases), ulcerative colitis (6 cases), upper respiratory infections (49 cases), arthralgias (28 cases), drug

ingestion (8 cases), inactive syphilis (4 cases), gonorrhea (4 cases), herpes zoster (1 case), measles and otitis media (1 case), eye disease (1 case), prostatic abscess (1 case), postoperative infection of the abdominal wall (1 case), axillary abscess (1 case) and peritonsillar abscess (1 case). Fourteen of fifty-five available chest roentgenograms revealed positive intrathoracic findings. Twelve showed slight to moderate enlargement of the nodes, three with calcification. Pulmonary abnormalities were noted in 5 cases: resolving pneumonic process, pneumonic infiltration, exaggerated pulmonic markings, miliary tuberculosis and fibrocalcific tuberculosis. Tuberculin tests, which were performed on 12 of the 14 patients, were positive in 11. The patients whose roentgenograms showed intrathoracic adenopathy or pulmonary infiltration, or both, had associated disease of the respiratory tract that could account for the abnormalities and often obviously did. In the cases in which the development of erythema nodosum was associated with ulcerative colitis, prostatic abscess, peritonsillar abscess, rheumatic heart disease, gonorrhea, conjunctivitis, postoperative infection, axillary abscess, measles and otitis media and ingestion of drugs the chest roentgenograms failed to demonstrate any pulmonary changes or intrathoracic lymphadenopathy.

Mebaral in Treatment of Epilepsy.—According to Cohen and Myerson, the drug known in this country as mebaral was introduced in Europe under the name of prominal, the chemical formula being n-methyl-ethyl-phenyl barbituric acid. It has been used in Europe quite extensively. After reviewing the results obtained by some European and British observers the authors say that this drug seems by far the best sedative in agitated depressed and anxiety states, since it produces more tranquillity and less narcosis than any other drug, and without untoward symptoms unless given in doses above 0.4 to 0.6 Gm. (6 to 9 grains) a day. The authors think that the drug is particularly useful for epileptic children who prefer tasteless medication, for psychotic epileptics who must be treated by medication concealed in their food, for patients who cannot be given adequate phenobarbital because of toxic drowsiness and, finally, for trial on patients who do not show satisfactory response after trials of phenobarbital, phenytoin and bromides, separately or in combination. In certain cases relatively refractory to other medication, signficant improvement was noted when mebaral was utilized. Mebaral was found to be less productive of toxic symptoms than phenobarbital or phenytoin, and a proportionately higher dosage was continued with safety and as great or greater clinical effectiveness. In the private practice of one of the authors mebaral has become the drug of first choice for the treatment and control of grand mal and petit mal. In cases in which it does not work well by itself, it combines well with phenytoin. In cases in which it is not effective, it is discarded, and phenobarbital and phenytoin in combination are used.

New Jersey Medical Society Journal, Trenton

39:465-516 (Sept.) 1942

*Segmental Enteritis. C. M. Robbins and O. H. Dreskin, Newark.—p. 473.
Possibilities and Practice of Chemotherapy in Wartime. J. S. Lockwood, Philadelphia.—p. 479.
Interstitial Keratitis. E. S. Sherman, Newark.—p. 485.
Diagnosis of Gallbladder Disease. L. L. Perkel, Jersey City.—p. 488.
Spontaneous Subarachnoid Hemorrhage: Analysis of Fifty Cases. B. A. Hirschfield, Trenton; A. S. Tornay and J. C. Yaskin, Philadelphia.—p. 494.
Intensive Arsenotherapy of Syphilis in New Jersey Hospitals: Presentation of Record Form for Essential Data on These Cases. M. I. Roemer, Trenton.—p. 498.
Management of Toxemias of Pregnancy. C. H. Ill, Newark.—p. 502.

Segmental Enteritis.—Robbins and Dreskin subjected 4 patients with regional enteritis to primary resection and transverse ileocolostomy. The first patient, a poor operative risk on admission, died on the thirty-sixth postoperative day of exhaustion, fecal fistula and subphrenic abscess. Two were discharged in two weeks in good condition with no complications except milk diarrhea in 1. The last 1, discharged after five weeks of convalescence, is free from symptoms at present. After review of the literature and of their experiences the authors believe that their first patient might have had a successful outcome with a simpler procedure of transverse ileocolostomy with exclusion and abdominal chemotherapy. The fact that 2 of the patients had had an appendectomy is in agreement with Shapiro's review, which revealed that 112 of 413 patients had had an appendectomy. Therefore when patients with an appendectomy scar continue to have lower intestinal complaints segmental enteritis must be considered in the differential diagnosis.

New York State Journal of Medicine, New York

42:1695-1790 (Sept. 15) 1942

New Aspects of Tuberculosis: The General Practitioner's Key Role. E. Mayer, New York.—p. 1723.
War Neuroses. K. M. Bowman, San Francisco.—p. 1729.
Hyperemesis Gravidarum. E. C. Hughes, Syracuse.—p. 1732.
Syphilis and Cancer: Reported Syphilis Prevalence Among 7,761 Cancer Patients. M. L. Levin, L. C. Kress and H. Goldstein, Albany.—p. 1737.
The Blood Bank. A. Korkosz, Schenectady.—p. 1746.
*Malaria in Infancy. H. A. Reisman, Jamaica, and H. Schneck, New York.—p. 1751.
Silent Mastoiditis, with Special Reference to Chemotherapy. G. D. Wolf and B. Capus, New York.—p. 1755.
Problems of Obstetric Anesthesia in the Average Hospital. J. A. Kalb, Endicott.—p. 1760.

Malaria in Infancy.—Reisman and Schneck report the case of quartan malaria in an infant of 3 months which presented the problem of whether or not the malaria was a true congenital infection. At delivery there was no present known history of malaria in the mother. The infant's infection may have been congenital by way of the placenta or acquired when 20 cc. of the mother's blood was given intramuscularly because of a difficult delivery. The mother had a history of infection and an apparent cure ten years previously with no apparent subsequent symptoms. The symptoms and signs of malaria in the infant subsided after quinine therapy was instituted.

North Carolina Medical Journal, Winston-Salem

3:485-538 (Sept.) 1942

Sex Hormones in Obstetrics and Gynecology. A. Grollman, Winston-Salem.—p. 485.
Suggested Program for Preventive Inoculations. F. H. Richardson, Black Mountain.—p. 488.
Intracutaneous versus Subcutaneous Vaccination: Comparison of Immunologic Responses to Both Methods. D. S. Martin, Durham.—p. 492.
Further Experiences with Technic of Administering Blood and Other Fluids via Bone Marrow. J. F. O'Neill, Winston-Salem; L. M. Tocantins and A. H. Price, Philadelphia.—p. 495.
The Criminal Insane. J. W. Ashby, Dix Hill.—p. 500.
Study in Contraception: Report of Birth Control Clinic, Two Years' Operation. Irma Henderson-Smathers, Ashville.—p. 501.

Northwest Medicine, Seattle

41:295-330 (Sept.) 1942

Hypertension: Follow-Up Study of 481 Patients. R. L. King, T. Carlile and J. M. Blackford, Seattle.—p. 298.
Dizziness from Hypertension: Controlled by Histamine Phosphate. W. Marshall, Appleton, Wis.—p. 305.
Urticaria. J. E. Strech, Seattle.—p. 309.
Recent Advances in Surgery: Their Clinical Applications. J. A. Gius, Portland, Ore.—p. 312.
Diagnosis of Paresis with Negative Spinal Fluid. W. B. Dublin and R. W. Brown, Fort Steilacoom, Wash.—p. 316.
Traumatic Rupture of Kidney: Report of Late Results. H. D. Norris, Seattle.—p. 317.
Subacute Cor Pulmonale: Due to Metastatic Carcinomatous Lymphangitis of Lungs. J. J. Krygier and I. C. Brill, Portland, Ore.—p. 319.

Ohio State Medical Journal, Columbus

38:797-892 (Sept.) 1942

Recent Trends in Treatment of Rheumatoid Arthritis. R. H. Freyberg, Ann Arbor, Mich.—p. 813.
Notes on Etiology and Therapy of Polyneuritis. C. D. Aring, Cincinnati.—p. 821.
Refrigeration of Gangrenous Extremities Before Amputation: Report of Case. W. Eggers, Cleveland.—p. 826.
Daily Weight in Management of Congestive Heart Failure. J. I. Goodman, J. F. Corsaro, L. C. Kousuth and L. W. Whiting, Cleveland.—p. 830.
Influenzal Meningitis: Review of Treatment of Fourteen Children with Type B Influenza Bacillus Meningitis. A. Schwinger, Cincinnati.—p. 835.
Brief Historical Sketch of Epilepsy. J. L. Fetterman, Cleveland.—p. 838.
A Pathologist Sees Colombia. W. M. Gerhan, Cincinnati.—p. 841.
Acute Adrenal Cortical Insufficiency. T. C. Laipply, Cincinnati.—p. 845.
Current Thinking in Field of Nutrition. J. Forman, Columbus.—p. 847.

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Public Health Reports, Washington, D. C.

57:1235-1286 (Aug. 21) 1942

Distribution of Health Services in Structure of State Government: VI. Medical and Dental Care by State Agencies—Continued. J. W. Mountin and Evelyn Flook.—p. 1235.

57:1287-1326 (Aug. 28) 1942

Evaluating Dental Health Programs. J. W. Knutson.—p. 1287.
Studies in Uric Acid Clearance. E. J. Stieglitz.—p. 1306.
Note on Toxic Principle in Eggs of the Tick Dermacentor Andersoni Stiles. E. A. Steinhaus.—p. 1310.

57:1327-1362 (Sept. 4) 1942

Technic for Staining, Dissecting and Mounting Male Terminalia of Mosquitoes. W. H. W. Komp.—p. 1327.
*Data on Concurrence of Death from Tuberculosis, Influenza and Pneumonia, Cancer and Heart Diseases Among Husbands and Wives. A. Ciocco.—p. 1333.
Additional Highly Virulent Strains of Rocky Mountain Spotted Fever Virus Isolated in Georgia. G. D. Brigham and J. Watt.—p. 1342.
Disabling Morbidity Among Male and Female Industrial Workers During 1941 and Among Males During First Quarter of 1942. W. M. Gafafer.—p. 1244.

57:1363-1398 (Sept. 11) 1942

Location and Movement of Physicians, 1923 and 1938: General Observations. J. W. Mountin, E. H. Pennell and Virginia Nicolay.—p. 1363.
Rickettsia-like Organism from Normal Dermacentor Andersoni Stiles. E. A. Steinhaus.—p. 1373.
Studies on Duration of Disabling Sickness: II. Duration of Disability from Sickness and Nonindustrial Injuries Among Male Workers; Disabilities Lasting One Calendar Day or Longer. W. M. Gafafer and Elizabeth S. Frasier.—p. 1378.

Concurrence of Death from Certain Diseases Among Spouses.—According to Ciocco, the records of 2,346 policyholders, referring specifically to the cause of death of 2,346 parental couples, reveal that the relative number of persons who die from the same cause as the spouse is significantly higher when the spouses died of tuberculosis, influenza, pneumonia or cancer than when they died from other causes. With tuberculosis the number is three to six times as high among spouses of persons who died of tuberculosis as compared to spouses of persons who died from other causes. With respect to influenza, pneumonia and cancer the number is one and four-tenths to one and eight-tenths times as high among the spouses of persons who died of these diseases as for the spouses of persons who died from other causes. The data do not corroborate the marital association regarding mortality from heart disease.

Rocky Mountain Medical Journal, Denver

39:597-660 (Sept.) 1942

The Art of Medicine. R. W. Fouts, Omaha.—p. 615.
Salpingitis. G. Heusinkveld, Denver.—p. 618.
Neurocirculatory Asthenia—N. C. A. L. W. Frank, Denver.—p. 621.
Repair of Penoscrotal Hypospadias. H. Buchtel, Denver.—p. 624.

South Carolina Medical Assn. Journal, Florence

38:235-256 (Sept.) 1942

*Some Observations on Bacterial Meningitis. M. H. Roberts, Atlanta, Ga.—p. 235.
Human Pyramidal Tract: VI. Evaluation of Pyramidal Syndrome. A. M. Lassek, Charleston.—p. 243.
Effects of War on Medical Service in Twelve South Carolina Counties with Limited Medical Personnel. M. I. Pickens, Charlotte, N. C.—p. 245.

Bacterial Meningitis.—Since Roberts has employed intensive chemotherapy, 7 patients with bacterial meningitis have come under his care and only 2 have died. The ages of the living children were 8, 5 and 3 years, 16 months and 10 months. The 2 children who died were 12 and 9 months old, respectively. This experience and that of others indicates that chemotherapy is the treatment of choice. Favorable reports have been published with the use of sulfanilamide, sulfapyridine, sulfathiazole and sulfadiazine. Because of the tendency of the infection to relapse, medication should be continued for ten to fourteen days after the spinal fluid is normal. High concentrations of the drug, 40 mg. and more per hundred cubic centimeters of blood, are tolerated by the host and may be the important factor in sterilizing the spinal fluid. The author's failure to sterilize the spinal fluid of 1 of the infants with influenzal meningitis who died with concentrations as high as 92 and 78 mg. per hundred cubic centimeters in the blood and spinal fluid, respectively, seems to indicate drug resistance.

Southwestern Medicine, El Paso, Texas

26:249-286 (Aug.) 1942

Treatment of War Burns. E. P. Palmer and E. P. Palmer Jr., Phoenix, Ariz.—p. 251.
The Nasopharynx. A. J. Ridges, Salt Lake City.—p. 255.
Arteriosclerosis and Hypertension (Resulting from Disturbed Acid-Base Equilibriums). R. de R. Barondes, Los Angeles.—p. 261.
Medicine and the Antitrust Act: Discussion of Government's Suit Against the American Medical Association. W. H. Hamilton, New Haven, Conn.—p. 266.

Surgery, St. Louis

12:345-522 (Sept.) 1942. **Partial Index**

Trends in Treatment of Burns. G. C. Penberthy, Detroit.—p. 345.
Utilization of Pedicle Skin Grafts in Correction of Cicatricial Anal Stenosis. W. H. Cole and P. W. Greeley, Chicago.—p. 349.
Effect of Topical Application of Several Substances on Healing of Experimental Cutaneous Wounds. B. E. Brush and C. R. Lam, Detroit.—p. 355.
Carcinoid Tumors of Stomach. K. E. Lemmer, Madison, Wis.—p. 378.
Subtotal Gastric Resection for Peptic Ulcer: Report of 230 Cases. G. G. Miller, Montreal, Canada.—p. 383.
Primary Sarcoma of Duodenum: Resection with Head of Pancreas by One Stage Whipple Operation. J. D. Bisgard and R. M. Cochran, Omaha.—p. 388.
Use of Sulfonamides in Treatment of Compound Fractures. C. L. Mitchell, Detroit.—p. 403.
Postoperative Thrombophlebitis and Embolism. N. W. Barker and J. T. Priestley, Rochester, Minn.—p. 411.
Aspiration Bronchopneumonia. C. W. Apfelbach, Chicago.—p. 413.
Concussion of Lung. J. D. King, Columbus, Ohio.—p. 415.
*Familial Hemolytic Jaundice: Study of Results of Surgical Therapy. C. W. McLaughlin Jr., Omaha.—p. 419.
*Chronic Biliary Typhoid Carriers. F. A. Culler and P. Crabtree, Ann Arbor, Mich.—p. 426.
Clinical Experience with Sodium Chloride Replacement. F. H. Power, S. Pedersen and W. G. Maddock, Ann Arbor, Mich.—p. 438.
Nonasphyxial Nitrous Oxide Anesthesia. W. O. McQuiston and S. C. Cullen, Iowa City.—p. 459.
Subdural Air: Preliminary Report of Its Use as Method of Preventing Postoperative Corticomeningeal Adhesions. W. W. Woods and E. A. Kahn, Ann Arbor, Mich.—p. 471.

Familial Hemolytic Jaundice.—During the last five years McLaughlin encountered 30 cases of familial hemolytic jaundice and advised splenectomy in 16 because of clinical and laboratory evidence that the disease process was not latent. The 13 persons who accepted this advice and have successfully undergone splenectomy came from nine unrelated families. The average age of the 13 was 25 years, the oldest being 40 and the youngest 5. Females predominated in the ratio of 2:1. The main presenting symptoms were weakness, fatigue and jaundice in all but 2 patients. This is evidence of the constant destruction of blood and associated icterus. Fever, chills, nausea and vomiting were attendant symptoms of those admitted during the active phase of the disease. The spleen was readily palpable in each of the 13. The principal complications of familial hemolytic jaundice were acute hemolytic crises, or "crises of deglobulization." There is a tendency for several affected members in a family to experience these episodes within a few days of one another with a possible reduction of the erythrocytes below levels of one million. The sudden and striking increase in the cellular elements of the blood during splenectomy is one of the most interesting features of this condition. There was a uniform rise in hemoglobin during operation and in the hour following, which averaged 23.2 per cent. The erythrocyte counts correspondingly rose during this period. The average increase was 1,100,000 cells. Both the hemoglobin and erythrocyte readings then gradually fell during the next two days and then gradually increased to normal in almost every case at the end of the first postoperative month. The leukocyte counts also became elevated during splenectomy, but this leukocytosis gradually decreased during the postoperative period. These changes in the blood picture are characteristic of familial hemolytic jaundice during and following splenectomy. The probable explanation is a sudden outpouring of cells into the peripheral circulation from an enlarged splenic reservoir which is compressed and manipulated during the surgical procedure. This initial autotransfusion is the factor which permits successful splenectomy in the presence of profound anemia or a crisis without resorting to transfusions. Following splenectomy, transfusion is safe but is rarely necessary. There has been no recurrence of the hemolytic factor in any of the 13 patients following splenectomy. If hemolysis reappears after splenectomy it may be assumed that the original diagnosis was incorrect, that overlooked splenic tissue has become active or that hemolymph nodes have hypertrophied and assumed a hemolytic character.

Chronic Biliary Typhoid Carriers.—Coller and Crabtree state that until the chronic typhoid carrier is recognized and completely managed or cured epidemic typhoid will continue to exist. The four places in the human body in which typhoid bacilli may remain and give rise to the carrier state are the urinary bladder, the intestinal mucosa, the biliary radicles of the liver and the gallbladder. Chronic carriers are those who harbor microbes for a year after infection. At present in Michigan there are 275 carriers on the typhoid registry, but on the basis of some statistics there should be around 3,600 designated carriers. This may be high, but when one considers that 2 to 4 per cent of all typhoid patients become permanent carriers it is a most probable figure. There are four methods to eliminate and control these unfortunates: negative stool and bile specimens, routine examination of urine and stool specimens from all food handlers, epidemiologic investigation of all sporadic cases of typhoid and routine examination of fecal or urine specimens from patients suffering from other illnesses and the culturing of bile from all gallbladders removed at operation. As regards their treatment at present in Michigan the eligibility criteria for operation and release of chronic biliary typhoid carriers are as follows: For a carrier to be operated on primarily for the cure of the carrier state he must be a chronic bile carrier and a good surgical risk. The eligibility criteria for release after cholecystectomy are twelve consecutive negative feces specimens obtained at monthly intervals and one negative bile specimen obtained during the postoperative year. Since 1937 the authors have studied 21 chronic biliary typhoid carriers before and after operation. The gallbladder of each was examined pathologically after its removal, and evidence of some chronic inflammation was found in all. The authors feel that 16 of the patients are definitely cured, though release bile specimens are not at hand for all of them. In 3 additional patients, who flave had their operations recently, the first several stool specimens have been negative and no doubt in time they will be classed as cured. The 2 patients who are not cured probably belong to that small group of carriers in whom the biliary radicles of the liver are infected. The postoperative bile specimens have been positive in both. From an analysis of stool cultures obtained after operation in the cured group two types of chronic biliary typhoid carriers were revealed: one in which the gallbladder alone was the focus of infection and one in which there were apparently smaller additional foci in the intestinal or the biliary tract. In the former the stool cultures become free of typhoid bacilli soon after operation. In the latter there is a definite delay (up to two hundred and sixty-seven days). Apparently, the additional foci were freed of typhoid bacilli by the powers of the body alone after the major source of the infection, the gallbladder, had been removed. In such patients a trial of one of the sulfonamides is suggested in the hope that it may hasten the destruction of any remaining typhoid foci within the intestinal tract.

Texas State Journal of Medicine, Fort Worth

38:305-362 (Sept.) 1942

Emotional Origin of Physical Symptoms in Children. H. Ford and L. Rose, Galveston.—p. 310.
Bronchoscopic Diagnosis and Treatment of Respiratory Disorder of Early Life. G. S. McReynolds, Galveston.—p. 314.
Diagnosis and Management of Common Juvenile Skin Diseases. E. B. Ritchie, Galveston.—p. 319.
Local Use of Sulfathiazole in Certain Staphylococcic Infections of Skin. B. P. York, Houston.—p. 322.
X-Ray Diagnosis of Thoracic Suppuration in Children. F. Y. Durrance, Houston.—p. 324.
Preoperative and Postoperative Pediatric Care. J. W. Duckett, Dallas. —p. 327.
Oral Malformations as Seen in Pediatrics. C. P. Jasperson, Corpus Christi.—p. 330.
Administration of Fluids to Children. C. A. Stewart, New Orleans. —p. 332.
Some Unattained Objectives in Pediatrics. W. D. Brown, Beaumont. —p. 335.
Use of Neoarsphenamine in Conjunction with Sulfathiazole in Treatment of Staphylococcic Septicemia. R. L. Moore, Dallas.—p. 338.
Complications of Prematurity: Prevention and Treatment. F. A. Garbade, Galveston.—p. 342.
Dental Caries and Malocclusion—Their Prophylaxis and Management. B. Bell, Dallas.—p. 346.
Aims of Preventive Medicine. W. R. Houston, Austin.—p. 349.

FOREIGN

An asterisk (*) before a title indicates that the article is abstracted below. Single case reports and trials of new drugs are usually omitted.

British Heart Journal, London

4:57-120 (July) 1942

Curious Syndrome with Signs Suggesting Cervical Arteriovenous Fistula and Pulses of Neck and Arms Lost. T. Lewis and Joan Stokes.—p. 57.
The Conducting System of the Vertebrate Heart. F. Davies.—p. 66.
Sinoauricular Node: Historical Note. A. Keith.—p. 77.
Chest Leads in Congenital and Acquired Dextrocardia. J. S. Richardson. —p. 80.
Electrocardiographic Changes Due to Trauma. H. Barber.—p. 83.
Electrocardiogram in Friedreich Disease. W. Evans and G. Wright.—p. 91.
Intracardiac Tumors. J. L. Hamilton-Paterson and L. I. M. Castleden. —p. 103.

British Journal of Ophthalmology, London

26:385-432 (Sept.) 1942

Statistical Analysis of 3,219 Persons Certified Blind at the Regional Clinic for Certification of the Blind, Glasgow and Southwest Scotland During the Period 1929-1935 (Continued). J. Marshall and H. E. Seiler.—p. 385.

British Medical Journal, London

2:209-236 (Aug. 22) 1942

Late Rehabilitation of the Injured: Survey of Seven Years' Experience in Industrial Clinic. A. Miller.—p. 209.
*First Aid Prophylactic Treatment of Compression Syndrome ("Crush Syndrome"). D. H. Patey and J. D. Robertson.—p. 212.
Vaginismus: Its Management and Psychogenesis. Joan Malleson.—p. 213.
*Relapsing Fever in Addis Ababa. P. Robinson.—p. 216.
Mustard Gas Burns. J. Grant and T. F. Ritchie.—p. 217.

First Aid Prophylactic Treatment of Compression Syndrome.—Patey and Robertson believe that the crush syndrome may be due to loss of blood constituents from the circulation into the tissue of the injured limb rather than to a release of a toxin from a crushed limb. They therefore aimed at restoring extravasated fluid back from the edematous limb into the circulation by intermittent positive pressure up to 60 mm. of mercury. They treated 2 cases successfully. There is experimental support for the new conception, and routine treatment appears justified. For the application of the principle in first aid treatment an elastic web bandage of 3 inches is ideal. If this bandage is applied from below upward, stretched to double its unstretched length and each turn partially covers the previous turn so that only ¼ inch of the lower edge of the latter projects below the fresh turn, an approximate pressure of 40 to 60 mm. of mercury is obtained. The bandage should be applied direct to the limb without the intervention of clothing. The stretch can be assessed by marking the lower edge of the bandage at half inch intervals and then doubling the markings on application. The foot or the hand of the injured limb should be included in the bandage to avoid edema in any part of the limb. After admission to the hospital, if the bandage has been immediately and correctly applied no further local treatment is required. The bandage should probably stay on for some days and possibly then be reapplied at slightly less pressure. First aid parties should be taught to apply the bandage properly, and immediately the limb is released from compression.

Relapsing Fever in Addis Ababa.—Robinson states that 340 cases of relapsing fever were observed in Addis Ababa during the second half of 1941. That Spirocheta obermcieri was transmitted by the body louse was substantiated by the facts that mixed infections of relapsing fever and louse borne typhus were common, spirochetes were often found in crushed lice collected from patients with relapsing fever and ticks were not found, nor was there a single case in which the "tache noir" (the primary tick bite sore) was observed. All the patients were treated immediately and responded admirably to neoarsphenamine. In about 6 per cent malaria was concomitant and the quinine treatment did not interfere with the neoarsphenamine. Jaundice, hemorrhage from the mucous membranes, occasional bleeding in the central nervous system, edema, acute thyroiditis, parotitis, perisplenitis and pachymeningitis were the

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complications encountered. Relapses occurred in spite of treatment: in 16 per cent one relapse and in 4 per cent two relapses. The longest interval was twenty-seven days. One, two or three injections of neoarsphenamine were necessary. Hemorrhages, if severe, must be treated. The prothrombin time was prolonged in every instance, even if not complicated by hemorrhage. Vitamin K proved to be the ideal treatment. The author thinks that 5 to 10 mg. of menadione in oily solution intramuscularly should be given to all patients with relapsing fever to prevent hemorrhage. The case mortality was 3.5 per cent, and at necropsy perisplenitis was present in almost every instance and sometimes splenic infarcts. Endocarditis was common.

Journal of Physiology, Cambridge

101:137-256 (Aug. 18) 1942

Effects of Drugs, Sugars and Allied Substances on Isolated Small Intestine of Rabbit. W. Feldberg and O. M. Solandt.—p. 137.
*Diuretic Action of Alcohol in Man. M. Grace Eggleton.—p. 172.
Effects of Trimethylamine on Growth and Sexual Development in Rat. H. Wastl.—p. 192.
Cholinergic Nature of Nerves to Electric Organ of Torpedo (Torpedo Marmorata). W. Feldberg and A. Fessard.—p. 200.
Determination of Plasma Volume by Evans Blue Method. A. C. Croake and C. J. O. Morris.—p. 217.
Interrelation of Prostigmine, Adrenalin and Ephedrine in Skeletal Muscle. Edith Bulbring and J. H. Burn.—p. 224.
Action of Oxytocic Hormone of Pituitary Gland on Urine Secretion. A. M. Fraser.—p. 236.
Effect of Histidine on Histamine Shock. O. G. Edholm.—p. 252.

Alcohol Diuresis in Man.—Eggleton determined the diuretic action of alcohol and its mode of action by simultaneous analysis of the concentration of alcohol in the blood and urine of 5 subjects. The diuresis following an alcoholic drink was roughly proportional to the amount of alcohol present when volume and other constituents were maintained at a constant level. Variations in external temperature seriously affected this relationship; that is, cold caused a greater diuresis. Its onset was delayed for twenty to thirty minutes after the drink was taken, and its height was unrelated in time to the peak of blood-alcohol concentration. The diuresis could be completely inhibited by solution of posterior pituitary. It was initiated by the increase in blood-alcohol concentration and failed to be maintained if this concentration was kept steady, even at a high level. The degree of diuresis from a given dose of alcohol varied widely in different subjects and was dependent on the natural rate of absorption of alcohol and water and possibly on a variation in the sensitivity of the pituitary mechanism. The diuretic response to alcohol and that of the cerebral cortex differed in one respect: the latter was most affected by the rate the concentration of alcohol in the blood was increased. The greater this increase was, the greater was the disturbance of function at any absolute concentration; but with the diuretic response the duration of the increase and not the rate of increase was important. When an equilibrium has been established in the body the concentration of alcohol in the urine remains 30 to 35 per cent higher than that in the blood. Comparison of these values with the arterial and venous blood and plasma indicated that the alcohol in the urine was in equilibrium with that in the water of plasma.

Lancet, London

2:145-174 (Aug. 8) 1942

Pneumonia Treated with Sulfapyridine and Sulfathiazole: Concentration of Drugs in Blood. Freda K. Herbert, E. F. Dawson-Walker and W. G. A. Swan.—p. 145.
Grave Anemias in Pregnancy and Puerperium: Report of Seventeen Cases. F. G. Lescher.—p. 148.
Electrical Convulsion Therapy: Clinical Observations. R. E. Hemphill.—p. 152.
Measuring Cerebrospinal Fluid Pressure. P. W. Nathan and C. W. M. Whitty.—p. 154.
*Air Entry Through Transfusion Sets. M. B. Devas.—p. 154.
Liver Abscess Following Perforated Duodenal Ulcer. K. W. G. Heathfield.—p. 155.

Air Entry Through Transfusion Sets.—Recently several deaths from air embolism following transfusion were encountered by Devas. Under certain conditions large quantities of air can be pumped into a vein through a transfusion apparatus working solely by gravity. For preventing such an eventuality he suggests that the screw clamp, instead of being on the rubber tubing between the blood bottle and the drip chamber, should be clamped on the tubing only 2 or 3 cm. above the needle in the vein. In this position the rate of flow is just as easily controlled, but in addition there will be a positive pressure in the apparatus above the clamp and any leak occurring will cause fluid to flow out and not air to flow in.

2:175-204 (Aug. 15) 1942

Fractures of Os Calcis. A. S. B. Bankart.—p. 175.
*Incidence of Neurosis in England Under War Conditions. A. Lewis.—p. 175.
Radiography of Femoral Neck. F. P. Fitzgerald and K. C. Clark.—p. 183.
*Development of Hypochromic Anemia During Pregnancy: Response to Iron Therapy. H. A. Hamilton and Helen Payling Wright.—p. 184.

Neurosis in England Under War Conditions.—According to Lewis, it is not easy to decide whether a mental disturbance is directly attributable to war conditions and particularly to air raids. It is therefore more informative to find out whether there is more or less neurosis altogether since the war or since the intensive air raids than to count up the cases that seem to have been caused by the war. Data have been collected in different British cities by doctors, hospitals and outpatient clinics. In the summary it is stated that air raids have not been responsible for any striking increase in neurotic illness. Crude figures from hospitals and outpatient clinics even suggest a considerable drop; the figures of the Ministry of Pensions, however, give a better indication of the problem. Reliable data from London and Bristol, and the impressions of medical observers, indicate that after intensive raids there is a slight rise in the total amount of neurotic illness in the affected area, occurring chiefly in those who have been neurotically ill before. Neurotic reactions may not show themselves for a week or ten days after the bombing; they usually clear up readily with rest and mild sedatives. Hysteria is uncommon; anxiety and depression are the commonest forms of upset. The incidence of neurotic illness has been low in firefighters and other workers in civil defense. Insanity has not increased, as far as figures are to hand, though more persons with senile deterioration have been admitted to mental institutions than before, because their relatives could not any longer look after them or because the raids had in other ways disturbed their routine and their precarious adaptation. The same was true of some defectives. Suicide has diminished in Scotland, especially among the middle aged and elderly. Figures for England and Wales are not available. It is impossible to distinguish between neurotic illness due directly to air raids and that which may follow such secondary troubles as disruption and loss of one's home, evacuation, difficulties in transport to and from work, or temporary loss of employment. It is to the war as a whole, with its accumulated stresses, that people have had to adjust themselves, and signs of failure to do this can be taken as warning signals of neurosis. An increase in alcoholism would be such a sign; there is no evidence that there has been any increase of this sort. The rise in road and industrial accidents has been considerable; many causes are at work, the psychologic ones among which have not been analyzed. There has similarly been a rise in juvenile delinquency: this cannot be regarded as tantamount to a rise in juvenile neurosis, but it suggests that the same environmental factors are at work as conduce to neurosis.

Hypochromic Anemia During Pregnancy.—Hamilton and Wright believe that physiologic changes in blood volume and the demands of the fetus on maternal iron reserves render hypochromic anemia especially frequent during pregnancy. The characteristic decrease in hemoglobin percentage, unaccompanied by a fall of the same degree in the red cells, makes the estimation of hemoglobin the best guide to the adequacy of the woman's iron reserves. The object of the present investigation has been to determine whether the current wartime dietary restrictions have had any detrimental effect on the hemoglobin concentration of the blood of women during pregnancy. Repeated hemoglobin estimations by the Haldane method have been carried out on 392 pregnant women from about the third month of gestation until term. Half of the women examined were treated with medicinal iron throughout the period of observation, while the rest had no such medication. The average

initial hemoglobin percentages were 79 in the untreated and 75 in the treated group. The corresponding average terminal percentages were 70 and 77, so that iron administration converted a deterioration during pregnancy into an improvement. From comparison with other published figures it is concluded that women of the artisan class are more anemic than before the war. Iron preparations should be given as a routine during pregnancy, and antepartum clinics should help expectant mothers to select and prepare iron rich diets.

Medical Journal of Australia, Sydney

2:1-18 (July 4) 1942

*Studies on Value of X-Ray Therapy in Experimental Gas Gangrene Infection. E. Singer.—p. 1.

2:19-36 (July 11) 1942

Shock. H. Devine.—p. 19.

2:37-54 (July 18) 1942

Applied Physiology of Functional Disorders of Circulatory System. R. D. Wright.—p. 37.
Sighing Dyspnea and Hyperventilation Syndrome. M. D. Silberberg. —p. 38.
Effort Syndrome. C. H. Fitts.—p. 41.

Roentgen Therapy in Experimental Gas Gangrene Infection.—Experiments on mice infected intramuscularly in the thigh with Clostridium welchi and Clostridium septicum and then only irradiated or irradiated and also given a local application of sulfanilamide powder revealed to Singer that irradiation did not prolong their survival. The infecting dose and the amount of sulfanilamide were so adjusted that the infecting dose alone would kill all mice within twenty-four hours, while when it was injected with sulfanilamide only some of the animals died. Mice infected with culture alone or the ones injected with the culture and also given sulfanilamide were not benefited by roentgen therapy. In view of these results it is difficult to understand why certain clinicians report enthusiastically on roentgen therapy in the prevention and treatment of gas gangrene in human beings. The fact that Cl. welchi occurs as a normal saprophyte in the intestine, on the mucous membranes and on the skin of many normal people and that gas gangrene is rarely a primary infection of a wound makes it clear that misconceptions of the action of a therapeutic procedure can arise in various ways. Suppurating or clean wounds in which Cl. welchi or some other anaerobic bacillus can be demonstrated apparently respond satisfactorily to such treatment. Actually the gas gangrene organisms were present only as saprophytes and the wound would have healed without treatment. Irradiation favorably influences only low grade localized infections. However, sulfanilamide and antitoxic serum act favorably on the virulent type of gas gangrene infection. Serum acts only on the toxemia, while sulfanilamide kills or prevents the multiplication of bacilli. As the diffusion of the sulfonamides is slow and blood clots and dead tissue are not readily penetrated locally they would have more a prophylactic than a true therapeutic action. Furthermore, as their penetrative power varies considerably, local treatment of fully developed gas gangrene in which the bacilli are widely dispersed would be ineffectual. When used locally only the pure crystalline substances or some form especially suited for local application should be employed. Crushed tablets contradict all surgical principles: placing them in a wound after surgical débridement is nothing more than the introduction of foreign bodies into an area from which they were just removed.

Quarterly Journal of Medicine, Oxford

11:121-180 (July) 1942

Fibrous Dysplasia of Bone with Endocrine Disorders and Cutaneous Pigmentation (Albright's Disease). M. A. Falconer and C. L. Cope, with discussion of bone changes by A. H. T. Robb-Smith.—p. 121.
Pneumonia in Infants, Children and Adults. G. Ormiston, Dorothy Woodman and F. J. W. Lewis.—p. 155.

Tubercle, London

23:107-138 (May) 1942

Further Review of Tuberculosis in Wartime. F. Heaf and L. Rusby. —p. 107.

Helvetica Medica Acta, Basel

8:657-844 (Dec.) 1941. **Partial Index**

Diseases of Stomach from Military Point of View. L. Michaud.—p. 666.
*Diagnosis and Therapy of Gastric Diseases in Military Service. A. Haemmerli.—p. 691.
*Evaluation of Fitness of Gastric Patients for Military Service. M. Densle.—p. 722.
*Experiences with Gastric Patients in Military Service. H. Kapp.—p. 727.
*Functional Examination of Heart. M. Holzmann.—p. 733.
*Circulation and Vegetative Nervous System in High Altitude Flying. H. Meier-Müller.—p. 780.
Utilization of Duration of QRS in Electrocardiogram for Functional Examination of Heart. A. Neftel.—p. 809.
Myocarditis Experimentally Produced with Dick Toxin. M. Gukelberger.—p. 812.

Gastric Diseases in Military Service.—According to Haemmerli, gastric disorders present a difficult problem in military medicine because of their chronicity and tendency to relapse or to develop on the basis of a hereditary predisposition. The stomach is greatly exposed to the damaging influences of daily life, infectious diseases and chronic focal infections. The stomach is influenced more than any organ by the psyche and the sympathetic nervous system. Dyspepsia is the most frequent symptom of patients with gastric disorders. A review of the records of 500 patients with this symptom disclosed that 66 per cent had gastric disturbances, while in the other 34 per cent the primary disorder involved the liver, gallbladder, circulatory organs, kidney and other organs. The author reviews the results of the roentgenologic examination of the stomach in 1,608 military patients. Roentgenoscopy is indispensable in the diagnosis of ulcers. The form of the stomach, its tonus and peristalsis often give information about the sympathetic innervation of the organ. Roentgenoscopy is not reliable in the diagnosis of gastritis. Hyperacidity or hypoacidity should not be designated as a disease. A single fractionated gastric aspiration gives little information; only comparative tests over weeks or months are of value. Frequently the entire symptomatology consists of functional disturbances, a manifestation of an impaired innervation and often a part of a general dysfunction of the sympathetic nervous system. This dysfunction may be hereditary or acquired. The anatomic lesion, the ulcer, is only one aspect of the diathesis. Under military conditions, treatment must be limited to this anatomic lesion. In some ulcer patients the diathesis develops on the basis of a hereditary predisposition. There is a type of ulcer that is a sequel to vascular disease such as arteriosclerosis or syphilis. Inadequate chewing was the causal factor in about 14 per cent of cases of gastritis. Correction of dental defects and improvement of hygiene of eating will counteract these disorders. Heavy meals immediately after great exertion may lead to gastritis. The military physician must see to it that when men are exhausted they receive easily digestible food. A heavy meal should be served only after they have recuperated to a certain extent. Abuse of nicotine is another frequent cause of gastritis. Whereas alcoholic gastritis has practically disappeared among soldiers, nicotine gastritis has greatly increased. The therapy of gastritis is difficult when a focal infection exists or after infectious diseases. Gastritis with anacidity represents an important group; the function of the mucosa must be investigated by a test meal. Gastric lavage in the morning has proved effective. There are soldiers with hypersensitivity to certain foods or with other allergic condition for whom effective treatment is hardly possible during active service. Approximately 15 per cent of patients with gastric disorders suffer from "nervous dyspepsia" and its sequels, which is a digestive disturbance produced by dysfunction in the vegetative nervous system, which in turn is brought on by a disturbance in the mental equilibrium or by disharmony in the organism due to faulty mode of living. Conditions connected with the person's occupation are often the provoking causes. Many cases of nervous dyspepsia can be readjusted by adoption of a more suitable mode of life. In some instances military service produces a desirable change and restores balance, in others it intensifies the existing disorder.

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Evaluation of Fitness of Gastric Patients for Military Service.—Demole reports that in November 1940, at a session of the gastroenterologists of Switzerland, a committee presented to the health service of the army rules to guide military physicians in estimating the service capacity of patients with gastric disorders. Patients with gastric tumor are to be definitely excluded from the army; also those who have undergone a gastric operation and who continue to have complaints. Some who have undergone gastrectomy or gastroenterostomy can be utilized in the army provided the necessary precautions are taken for their alimentation. The patient with a verified gastroduodenal ulcer is for a long time unsuited for military service. Acute duodenal ulcer may heal completely under attentive treatment. At the end of six months the patient can be examined again for a new decision. A radiologic niche on the small curvature of the stomach is more refractory, and a man with such a lesion cannot return to the service for about two years. Patients with chronic ulcer and periodic recurrences must be excluded from the army in order to avoid the risk of serious complications. Nothing is more difficult than to declare an ulcer cured; the condition is likely to recur without apparent cause. Even the disappearance of the radiologic sign does not prove complete healing. Outside of the ulcer periods with regular postprandial cramps, the ulcer patient does not have an intact stomach. Gastritis is the rule in duodenal ulcer; the modifications of gastric acidity persist; the patient may have malaise, which cannot be ascribed to the ulcer as such. From 40 to 50 per cent of patients with dyspepsia have gastritis. They present a great variety of symptoms, and the roentgenologic aspect and chemism rarely provide conclusive evidence. Only gastroscopy gives information regarding the condition of the mucosa. In acute gastritis appropriate dietetic treatment may result in a cure. In chronic gastritis numerous etiologic factors may be encountered: irritation by tobacco or alcohol, tachyphagia and insufficient mastication; abdominal disorders such as appendicitis, cholecystitis and adnexitis, and focal infections such as paradentosis and tonsillitis. In these cases military life may transform an old but latent dyspepsia into a more acute type. Severe forms of anacid atrophic gastritis resistant to treatment render a subject unsuitable for service. In patients with functional disturbances a thorough examination is essential in order to rule out an organic lesion and determine the nature of the disorder. In the presence of a nervous dyspepsia with absence of organic lesions and a tendency to neuropathia a psychiatric analysis might be advisable.

Gastric Patients in Military Service.—According to Kapp, roentgenoscopy is the most important method in the diagnosis of gastric disorders. Negative roentgenoscopy does not necessarily indicate that there is no gastric disorder. The most frequent stomach lesion, gastritis, is only rarely detected by roentgenoscopy. Fractional aspiration of the gastric contents is helpful in the diagnosis of gastritis, particularly if proper attention is given to the presence of cellular elements in the gastric juice. Estimation of fitness for military service is difficult in men with gastric disorders. The mental attitude of the patient is an important factor. It has been found that in the front line and during offensive warfare hemorrhages and perforations from ulcers are not more numerous than under more normal conditions. The close connections between the nervous system and gastric disorders are realized more and more. Many of the so-called gastric neurotic, however, have a gastritis or an ulcer. It is impossible to render a final decision regarding the fitness for service until the gastric disorder has been definitely identified. Attention must be given to the correct distribution of meals. German military physicians call attention to the fact that the morning and evening meals are often too small in comparison with the large noon meal. They recommend that the noon meal furnish about 40 per cent of the daily intake and the morning and evening meals 30 per cent each.

Functional Examination of Heart.—Holzmann demonstrates that the cardiac function is only the activity of one link in the chain of the circulatory organs and that circulation serves all life processes. The cardiac function becomes manifest in the minute volume and in the pressure. Both of these factors are to a great extent dependent on the other links in the chain of the circulatory system. On the other hand, a functional disturbance of the heart due to a myocardial impairment or to a defective mechanism may cause disturbances in the entire system. The numerous and close interrelations explain why the wish of the practitioner for a simple and universal functional test of the heart cannot be satisfied. From the clinical point of view a detailed history and a thorough examination are still the most essential factors in the estimation of the cardiac function. They can be supplemented by tolerance tests. Control of the pulse, the blood pressure, the respiration, the vital capacity and the electrocardiogram are important. They yield information that gives a better understanding of the functional capacity. The results of each individual test, however, are often equivocal and therefore easily misleading. If estimated together with other observations, they can be of value.

Circulation and Vegetative Nervous System in High Altitude Flying.—Meier-Müller directs attention to the importance of the cardiovascular system in determining fitness for military aviation. The heart and circulatory organs must be examined with all available methods. Orthodiagram, electrocardiogram, radioscopy and tests in the low pressure chamber are absolute necessities in estimating the flying capacity. The behavior of the cardiovascular system under the abnormal physiologic and psychologic conditions of a flight at high altitude must be determined in the presence of oxygen deficiency, of low temperatures (up to minus 60 C.), during great and rapid altitude changes, during accelerations up to 10 g (g = acceleration of gravity) and during the action of centrifugal and centripetal forces. The high altitude resistance test by means of the low pressure chamber may disclose the adequacy of the organic functions, but it would be a mistake to base estimation of fitness exclusively on clinical factors. Persons with healthy cardiovascular systems may fail under the exertions of wartime aviation, because "the nerves failed," because the man did not have the adequate psychic resistance, because during moments of greatest concentration and demands on the sense organs, during mental stress and reduced circulatory and respiratory function, he failed physically and mentally. A normal heart, normal circulation and normal respiration are of little value in military aviation if the person does not also have adequate intelligence, a normal brain, a solid nervous system and a maximal psychic resistance. The author directs particular attention to the correlations between sympathetic nervous system and psyche. It has been demonstrated that the vegetative regulation of blood distribution under the influence of high altitude and of great accelerations is to a great extent dependent on the mental clarity and the integrity of the aviator. It was believed that great vasolability rendered a person unfit for the flying service. That was erroneous. Today, vegetative stigmatism, for instance, in the form of increased emotional irritability is no absolute reason for exclusion from the flying service. On the contrary, some exploits in aviation, particularly in aerial combat, are accomplished by such emotionally hyperexcitable, vasolabile persons. A number of successful combat fliers exhibit a higher than average sensitivity of the vasomotor system. If vasomotor sensitivity is found in daring, keen and energetic personalities, it constitutes no hindrance to flying service. However, if it is associated with unsteadiness, superficiality and lack of responsibility, it is a cause for rejection.

Bol. Inst. de Med. Exper. p. Cancer, Buenos Aires

18:929-1320 (Dec.) 1941. **Partial Index**

*Electrosurgical Therapy of Cancer of Rectum. A. H. Roffo and F. Carranza.—p. 1027.

Electrosurgical Therapy of Cancer of Rectum.—Roffo and Carranza treated 926 patients with cancer of the rectum. They advocate surgical therapy whenever the local lesion can be removed, regardless of metastases in remote organs, provided the general condition of the patient is satisfactory and there are

no contraindications. Operability and the type of operation are decided by a surgical exploration in the course of which inflammatory adhesions of the tumor are severed and the tumor can be seen and sometimes palpated. The prognosis is good when the tumor cannot be palpated or when it is palpated with difficulty. Local metastases, perforation of carcinoma into the peritoneum and involvement of the prostate, the uterus and the vagina do not constitute contraindications to a radical operation. Perforation of the tumor into the bladder, metastases in the peritoneum and diffuse metastases in the bones contraindicate either a radical or a palliative intervention. A radical sacral operation is the operation of choice in low ampullar and anorectal forms. When the tumor is situated above the peritoneal fold and there is a reasonable segment of normal tissue in the lower part, Hartmann's operation, by which the anorectal segment is not removed, is to be preferred. The authors employ the two stage operation. The first stage includes colostomy, examination of the rectum, lavage and high voltage roentgen therapy. In the second stage the rectum is exposed by the sacrococcygeal approach and the bowel is divided by electrocoagulation technic of Goetze and the tumor is electrocoagulated. The peritoneum is not opened. Inoperable cases thus treated may become operable. When this is not the case, the rectum is sectioned above the tumor, which is then coagulated and removed with the involved lower segments of the rectum including the anus, sphincter and fat of the perirectal space. The authors employed electrosurgical therapy in 261 cases with 50 per cent five year cures. There was an operative mortality of 2 per cent.

Revista Clínica Española, Madrid

4:1-80 (Jan. 15) 1942. **Partial Index**

Nutritional Needs of Human Organism. F. Grande Covián.—p. 1.
Two Cases of Addison's Disease Treated with Subcutaneous Implantation of Desoxycorticosterone Pellets. C. Jiménez-Díaz, J. Parra, E. Roda and A. Romero.—p. 20.
Partial Thenar Atrophy (Wartenberg). J. López Ibor.—p. 23.
"Hemorrhagic Allergy" and Tuberculosis. P. A. Buylla and J. G. Costa.—p. 28.
Factors Precipitating Eclampsia. F. Orengo Díaz del Castillo.—p. 35.
*Tuberculosis of Mesenteric Lymph Nodes in Adult: Grave Tumoral Forms. J. Calvo Melendro.—p. 39.
Hallopeau's Acrodermatitis Continua Pustulosa: Case with Recovery After Total Teleroentgenotherapy. J. Díaz de Rábago.—p. 51.
Indications for Therapy of Nontuberculous Pleurisy. E. Eizaguirre.—p. 57.

Tuberculous Mesenteric Lymph Nodes in Adults.—Abdominal lymph nodes may become tuberculous early in life just as mediastinal lymph nodes do. Tuberculosis of the mesenteric lymph nodes is a reaction to a visceral lesion at the port of entry of the tubercle bacillus. It does not necessarily appear during childhood. To make the diagnosis of primary infection possible, other organs must be carefully examined, because enlargement of lymph nodes may be present in other than the primary infection. In miliary tuberculosis, for instance, the tuberculous process may involve various groups of lymph nodes. Calvo Melendro differentiates several types of mesenteric lymph node tuberculosis. Clinical diagnosis of the primary lesion of the intestine is much more difficult than the diagnosis of the primary focus in the lung. Intestinal symptoms may be absent, palpation almost never succeeds, and roentgenoscopy is of no value in the beginning. Only after the lymph nodes have become calcified do they become visible in their typical location, which is the ileocecal angle. More or less localized abdominal pain may raise a suspicion. General symptoms such as fatigue, fever, general debility or loss of weight may direct attention to tuberculosis; localization may become possible in the presence of pain. The tuberculin reaction is important. The author observed the condition in 3 young soldiers. The men lived in rural regions until their entry into military service. They acquired the disease a short time after coming to a large city. The tuberculin reaction proved valuable in the diagnosis. In 2 of the patients the disease caused cachexia and terminated in death without dissemination of the tuberculous process. No information could be obtained regarding the outcome in the third case. The clinical features resemble the condition which the earlier authors designated as tabes mesaraica.

Acta Radiologica, Stockholm

23:1-110 (Feb. 28) 1942. **Partial Index**

*Lesions of Rectum and Bladder Caused by Radium Therapy of Cancer of Cervix Uteri. J. J. Chydenius.—p. 1.
*Mammography of Breasts with Pathologic Secretion. N. Frostberg.—p. 9.
Roentgen Findings in Intestinal Knots. J. Frimann-Dahl.—p. 22.
Contribution to Problem of Pyelovenous Reflux. H. Cederlund.—p. 34.
*Some Experiment and Clinical Lights on Rotation in Therapy, Its Basis and Possibilities. J. Nielsen and S. Hoeffer Jensen.—p. 51.
Roentgen Therapy in Lumbago. A. Clausen.—p. 67.
Isolated Fractures of First Rib. S. E. Sjögren.—p. 79.

Lesions of Rectum and Bladder Caused by Radium Therapy of Cancer of Cervix.—Chydenius reports observations on ray lesions of the urinary bladder, rectum and adjoining tissues following radium therapy of carcinoma of the uterine cervix in the course of treatment at the Central Institute For Irradiation in Finland during the years 1937 to 1940. There were 321 patients with carcinoma of the cervix uteri treated with radium or roentgen rays. Of these 33 exhibited late reactions on the rectum. The majority had mild changes in the rectal mucosa, but in 15 the lesions were severe. There were 4 cases with severe complications of the bladder. The distance between the tumor and the rectum varies greatly and, as a result, the doses of rays that reach the rectum are subject to great variation. Measurement of the dosage in milligram element hours is far from satisfactory in eliminating damage to adjacent structures. Variations in position of the rectum are demonstrable in roentgenograms. There is much room for improvement in the calculation of focus doses in radium as well as roentgen therapy. The author calls attention to his previous suggestions on isodoses computed in roentgens.

Mammography of Breasts with Pathologic Secretion.—According to Frostberg, secretion from the nipple of a nonlactating breast is sometimes the first sign of a pathologic process. There has been much discussion regarding the significance of such secretions. The suggestion that they indicate cancer has caused many unnecessary mastectomies. At the author's hospital at Norrköping, mammography has been employed since February 1939 for all breasts with pathologic discharge from the nipple. Fourteen mammographies have been done, and in all valuable information has been obtained as to the nature of the mammary process. The pictures were a valuable aid to the surgeon in cases in which resection was subsequently performed. The technic used was that described by Hicken in 1937. The contrast material required never exceeded 2 cc. Mammography should not be employed in inverted nipples because it usually fails. The author's attempts at mammography were unsuccessful in 4 cases. Mural papillomas and cysts were demonstrated. In 2 cases the roentgenogram suggested cancer. The value of mammography cannot be questioned.

Rotation Therapy.—Nielsen and Hoeffer Jensen describe their experience with rotation irradiation. Experimental measurements were made with small condenser chambers on a thorax phantom and on an anatomic specimen. The depth dose for small stationary fields of less than 50 sq. cm. was measured for various ray qualities. A number of intensity distribution curves were reproduced; they showed that a central zone forming a cylindric core about the axis of rotation receives a homogeneous dose considerably larger than that received by the surrounding peripheral zone. The fall in intensity from one zone to another is abrupt. The ratio of the maximum dose to the peripheral dose depends on the size of the field (the opening in the diaphragm) but is only to a limited extent dependent on the quality of the rays and the focus-axis distance. The authors relate their clinical experience with rotation treatment in 8 cases of cancer of the esophagus. As a result of the small size of the fields made possible by the constant screening control the general condition of the patients was little affected. Daily doses of 1,000 roentgens given twice were tolerated without difficulty. Even with a total dose of 22,000 roentgens in the course of four weeks only a moderate erythema was observed. The primary effect on the tumor was good and the stenosis was overcome. The possibility of applying the rotation therapy to other tumors (cancers of the uterus, the rectum and the hypophysis) is discussed and the value of the screening control emphasized.

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Book Notices

The Management of Fractures, Dislocations and Sprains. By John Albert Key, B.S., M.D., Clinical Professor of Orthopedic Surgery, Washington University School of Medicine, St. Louis, and H. Earle Conwell, M.D., F.A.C.S., Orthopaedic Surgeon to the Tennessee Coal, Iron and Railroad Company, Birmingham, Ala. Third edition. Cloth. Price, $12.50. Pp. 1,303, with 1,259 illustrations. St. Louis: The C. V. Mosby Company, 1942.

This book, written by two leaders in the field concerned, is especially valuable during the war. In the present edition extensive changes have been made in sections devoted to fractures of the spine, humerus, hip and foot. The chapter on compound fractures has been rewritten to include the great strides in chemotherapy. A section on war injuries has been added. There is an important chapter on the workmen's compensation law affecting fracture cases and another on the medicolegal aspects of fracture cases. The authors outline a list of the splints to be kept in a doctor's automobile and another list of splints to be kept in a doctor's office. These two lists are valuable especially in relation to civilian defense. The chapter on the principles of treatment of fractures is well done. Some of the best work of Colonel Kirk of the Medical Corps of the U. S. Army has been reproduced with many of his illustrations. Conwell's ladder splint is an effective device for emergency immobilization of fractures of the spine or pelvis and for visceral injuries. For compound fractures it is advised that the wound be exposed and a clean dressing applied at the earliest moment. This dressing not only lessens the bleeding but protects the wound from further contamination. If possible, this dressing should include sulfanilamide or sulfathiazole or preferably a mixture of the two. The powder should be sprinkled liberally into the wound. For this reason these drugs should be made available in emergency dressing stations and in industrial plants and should be carried in doctors' automobiles and ambulances which are sent out for the specific service of picking up injured persons.

In the section on débridement the authors outline ten important points: excision of the skin margin, enlargement of the wound, débridement of the wound proper, treatment of the bone, irrigation of the wound, repair of the deeper structures, reduction and internal and pin fixation of the fracture, final inspection of the wound and control of hemorrhage, chemotherapy of the wound and closure of the wound. The authors quote an interesting section on the avoidance of malpractice suits from a book entitled Court and Doctors by Stryker, who said that "the best way to avoid a lawsuit is not to deserve one." In the section on vertebral disk lesions the authors call attention to the wave of enthusiam for the removal of a disk from all patients with low back pain and sciatica. These patients should not be subjected to spinograms and intraspinal operations until conservative treatment has failed to relieve their symptoms. Figure 973 is an excellent illustration of the apparatus for the application of Russell traction in the treatment of fractures of the shaft of the femur. In the treatment of dislocations of the knee the authors do not advise open operations because the ligamentous damage is so extensive that there is little chance of operative repair and the chance is not worth the risk incident to the operation.

In spite of the fact that the book is so valuable, it deserves some constructive criticism. Some of the illustrations, especially photographs and several of the roentgenograms, could be improved. Some portions of the book, such as the section on the foot, are not up to par. March fracture is given slight mention, and the section on Freiberg's infraction of the metatarsal head is inadequate. All in all, this is an excellent book and one of the finest on the subject. It should be in the library of every physician and surgeon, especially during wartime, when the military aspects are so urgent and civilian defense so important.

The Answer is . . . Your Nerves. By Arnold S. Jackson, M.D., F.A.C.S. With a Chapter by the Rev. Edwin O. Kennedy. Cloth. Price, $2. Pp. 197, with illustrations by Evelyn Lipman. Madison, Wisconsin: Kilgore Printing Company, 1942.

This book, written for patients, comes from an author of wide experience, associated for many years with one of our largest clinics. He describes with accurate detail the hundreds of nervous patients, both male and female, who fill the clinic waiting rooms, almost to the exclusion of people with more structural evidence of disease. Case histories are cited, but many cover only a few days or weeks of the patients' illness, too short a time to evaluate the effects of therapy. Treatment is largely relaxation, particularly the muscular exercises of Jacobson, the back to the country type of change of environment, and common sense psychotherapy. There is some loose thinking, such as "Some men shout and work themselves up to high tension when talking over the telephone long distance. Such tension merely raises the blood pressure and hardens the arteries" (p. 11). One of the best remarks comes from Carl Hubbell, star pitcher for the New York Giants: "Baseball is a fast game, but you've got to slow down to play it. And life is that way, too, I think" (p. 13). The illustrations by Evelyn Lipman are clear and delightful although grossly exaggerated to make the points.

The book is a light but frontal attack on a major medical problem and should help those who read it seriously. Some will object to the emphasis on muscular relaxation, but this is often the best prelude to psychotherapy and, if used in this way, it becomes a kind of voluntary 'mental alienation,' to use Sister Kenny's phrase, between our brain and our muscles. We may, by putting the muscles in 'neutral' leave the brain more receptive to therapeutic ideas.

Microbiology and Man. By Jorgen Birkeland, Ph.D., Assistant Professor of Bacteriology, Ohio State University, Columbus. Being an Account of the Diverse Properties and Characteristics of Microorganisms, a Description of the Various Tools and Techniques for their Handling, and an Inquiry into their Subtle Relationships to Everyday Life. Cloth. Price, $4. Pp. 478, with 44 illustrations. Baltimore: Williams & Wilkins Company, 1942.

The author's preface states that this is "designed as an elementary textbook for the student who plans to take but one or two courses in microbiology. It is intended to serve as a basis for an understanding of the part played by micro-organisms in everyday life. It is a guide for learning as well as a source book of facts." The book is divided into four sections on fundamentals of microbiology, infection and resistance, common infectious diseases, and microbiology of food, milk, water, sewage and soil. There is an appendix classifying the Schizomycetes. There are also a useful glossary and several pages of references. There is much information contained in this book, but it is an unusual type of textbook in some respects. For example, the chapter on tuberculosis contains only one illustration, which is a rather poor reproduction of experimental tuberculosis of the spleen and liver of monkeys. There is no picture of the tubercle bacillus. Since this is a book on microbiology, one would expect the emphasis to be more on the bacteria themselves rather than on the diseases which they cause. In the way of minor criticism, the reviewer feels that it is a waste of ink to entitle the first chapter "By Way of Introduction" instead of plain "Introduction." Selective pruning and reemphasis in future editions should do much to improve this book.

The Principles and Practice of Medicine: Designed for the Use of Practitioners and Students of Medicine. Originally written by Sir William Osler, Bart., M.D., F.R.C.P. By Henry A. Christian, A.M., M.D., LL.D., Visiting Physician, Beth Israel Hospital, Boston. Fourteenth edition. Cloth. Price, $9.50. Pp. 1,475, with illustrations. New York & London: D. Appleton-Century Company, Inc., 1942.

Fifty years have passed since the publication of the first edition of this famous textbook. Its popularity at one time was such that it led all other textbooks on the practice of medicine in total sales. Since the death of Sir William Osler there has been a succession of rewriters and editors. The present edition has been completely rewritten and reedited, and the text has been changed to fit recent advances in medicine. Much of the material has been rearranged, and new material has been added, according to Dr. Christian, only after experience has indicated that it is worth while.

The present volume begins, interestingly enough, with a discussion of psychosomatic medicine, emphasizing the great importance of this new point of view in medical practice. In order to emphasize this still further, the first section of the book is devoted to functional diseases of the nervous system, recognizing those conditions that are essentially nonorganic in nature, at least as far as we now know. Here are considerations

of phobias and, incidentally, the use of the term neurasthenia as the preferred term for most of the disorders of this type. Strangely, however, the word psychoanalysis is not found in the index nor is there anywhere in this section of the book a specific reference to the freudian methods. Such methods are introduced in the discussion of hysteria with the recommendation that they be left to those who are especially trained in the field. The consideration of the infectious diseases begins with the pneumonias, and typhoid is now relegated to a place far along the list. However, the outline for typhoid may still serve as the ideal form for the discussion of any infectious disease. One finds the discussion of the common cold under the heading coryza definitely assigned to conditions due to viruses. The consideration of infantile paralysis is condensed and quite up to date. Particularly commendable in this edition are the excellent bibliographies presented in the most modern form, indicating the inclusion of important material practically up to the date of publication.

The literary style makes this book one of the most easily readable of all textbooks on the practice of medicine. The present edition may be highly commended as a great advance over the previous edition and one especially suited to the general practitioner.

A Short History of Cardiology. By James B. Herrick. Cloth. Price, $3.50. Pp. 258, with 48 illustrations. Springfield, Illinois & Baltimore: Charles C Thomas, 1942.

History in medicine, as in every other field of human activity, may be said to be composed of the lives of the men who have made history. Guided by this aphorism, Dr. Herrick has prepared a history of cardiology based on the lives of the greatest contributors to the study of the heart and of its changes. For Dr. Herrick, literature and the history of medicine have been enjoyable avocations. This enjoyment is reflected in the book, which is not a series of biographic sketches, such as one might find in a cardiologic "Who's Who," but a well written consideration of the contribution of each of the great investigators whose work is included with, from time to time, philosophical, animate versions. For instance, "It is true that Bouillaud had his shortcomings. One may shudder at his wholesale bleedings; one may smile at his rancorous criticism of others; one may regret his waste of time and energy in trivial contentions for the rather empty glory of priority. Overlooking these minor shortcomings, one must honor him for his persistent contention that his views were novel, sound and fundamentally of great importance." Again, "The term 'chronic myocarditis' crept into the literature and was in some respects far from clarifying because it was often applied to processes that were not inflammatory." The book is printed on a special stock, illustrated with portraits carefully chosen, and is worthy of a place in every medical library.

Psychodiagnostics: A Diagnostic Test Based on Perception. By Hermann Rorschach. Including Rorschach's Paper: The Application of the Form Interpretation Test. (Published Posthumously by Dr. Emil Oberholzer.) Translation and English edition by Paul Lemkau, M.D., The Henry Phipps Psychiatric Clinic, Baltimore, and Bernard Kronenberg, M.D. Editor: W. Morgenthaler, M.D. Second edition. Cloth. Price, $5.75. Pp. 226. New York: Grune & Stratton, Inc.; Berne: Verlag Hans Huber, 1942.

This work represents the second edition of the English translation of Rorschach's original papers by Drs. Bernard Kronenberg and Paul Lemkau. As the translators state in their preface, there is a fast growing interest in the Rorschach test and a need for more information concerning the original and basic work. The translators found the task of adequate translation exceedingly difficult, but it would appear that they have done an excellent piece of work.

The Rorschach test was devised and organized by Herman Rorschach, who was born in Zurich, Switzerland, in 1884 and died in 1922. His early death was a great loss to psychiatry in general and to Swiss psychiatry in particular. He was an extremely versatile man with a sound character and a practical grasp of scientific knowledge together with an inexhaustible interest in research. The Rorschach test, often referred to as the "ink blot test," is being used more and more for the differential diagnosis of personality problems. When given and evaluated by one who possesses a thorough knowledge of Rorschach's method and technic it offers an excellent guide relative to the prognosis and choice of treatment to be employed when some form of psychotherapy is indicated. The translation is intended primarily for students of the Rorschach technic, but the book should prove of interest to all students of human behavior. Any comprehensive discussion of the method itself or the evaluations and interpretations placed on the material collected when an individual is exposed to the Rorschach test is not practical if not quite impossible in a short review. Any one who is at all interested in attempts to measure or evaluate problems of human personality structure by means of academic laboratory methods is advised to study Rorschach's basic work very carefully. They seem to offer greater possibilities for accurate evaluation than any other method or methods that have been presented up to the present time. Improvements in the technic itself and evaluation of the material collected are constantly being worked out by Rorschach's followers.

Anatomy of the Human Body. By Henry Gray, F.R.S. Edited by Warren H. Lewis, B.S., M.D. Twenty-Fourth edition. Cloth. Price, $12. Pp. 1,428, with 1,256 illustrations. Philadelphia: Lea & Febiger, 1942.

A new departure in the twenty-fourth edition of this famous book is the addition to the editorial staff of six distinguished anatomists, who have assisted the editor in revising, rewriting and making additions of the latest information in their fields; yet the book has retained the familiar arrangement of chapters which has characterized it for many years. The six associate editors are Earl T. Engle, professor of anatomy, Columbia University College of Physicians and Surgeons, New York; Joseph C. Hinsey, professor of anatomy, Cornell University Medical College, New York; Normand L. Hoerr, professor of anatomy, Western Reserve University, Cleveland; Karl E. Mason, professor of anatomy, University of Rochester, Rochester, N. Y.; David M. Rioch, professor of neurology, Washington University, St. Louis, and Roy G. Williams, associate professor of anatomy, University of Pennsylvania, Philadelphia. Another innovation is the introduction of thirty roentgenograms in the chapter on surface and topographical anatomy, a belated recognition of the important role which roentgenography plays in anatomy. The forty-seven additional pages are accounted for in this way, by the introduction of other new illustrations and by the introduction of new text, particularly in the chapter on the central nervous system.

This edition also contains a picture of brief biographic data about Henry Gray, the original author. While still a medical student, Gray was awarded in 1848 a prize by the Royal College of Surgeons in England for an essay on "The Origin, Connections and Distribution of the Nerves to the Human Eye and Its Appendages." In 1852, when only 25 years of age, he was elected a fellow of the Royal Society and the following year was awarded the Astley Cooper Prize for an essay on "The Structure and Use of the Spleen." He had been demonstrator of anatomy, curator of the museum and registrar of anatomy at St. George's University in London and was a candidate for the position of assistant surgeon, when he contracted smallpox and died at the early age of 34. Henry Gray published the first edition of his anatomy in 1858. It contained 750 pages and 363 illustrations which had been drawn by H. Vandyke Carter, a good friend and demonstrator of anatomy at St. George's Hospital. These illustrations in no small part accounted for the success of the book from the start. A second edition was prepared by Gray two years later.

Psychotherapy in Medical Practice. By Maurice Levine, M.D., Attending Psychiatrist, Cincinnati General Hospital, Cincinnati. Cloth. Price, $3.50. Pp. 320. New York: Macmillan Company, 1942.

To attempt to evaluate psychotherapy and to present to the general medical practitioner the essence of psychotherapeutic concepts as a growing and dynamic part of psychiatry is by no means easy. Concreteness, simplification, the removal of the redundant and the elaboration of the complex material of psychoanalysis in terms that can be understood and used by the average medical man is the aim of the author of this book. In large measure he has succeded, but the size of his canvas tends to distract from the focal point, and details creep in only to confuse and not to clarify. Few men have time or energy, unfortunately, to visualize so vast and all embracing a picture and yet, given prolonged study, this work will repay

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the effort used. The opening chapters on such subjects as common misconceptions, methods for the general practitioner and suicide risks are particularly valuable. Those on sex and marriage and on normality and maturity toward the end of the book seem to be less useful, although most of the material presented is sound. References to the current literature are given and there is a good index. Case histories have been omitted, the author believing that most physicians would skip over them. Doctors as a rule are brought up on case histories and, in the opinion of the reviewer, a few pertinent ones showing end results, with less academic discussion would enhance the value of the book and enable the author to make his points in a more succinct and penetrating manner.

El diagnóstico de los tumores suprarrenales. Por el Dr. Octavio M. Pico Estrada, professor adjunto de la Facultad de medicina, Buenos Aires. Paper. Pp. 156, with 4 illustrations. Buenos Aires: Librería y Editorial "El Ateneo," 1940.

In this special work the author encompasses the subject of diagnosis of adrenal tumors. He points out the local symptoms that adrenal neoplasms produce and their roentgenologic peculiarities. Hypertensive syndromes, the adrenal-genital symptom complexes and the syndrome known as Addison's disease as well as the rare forms of clinical entities accompanied by fever are thoroughly described and evaluated. In chapter IX the author discusses the relationship between the clinical syndromes enumerated and the histologic structure of the tumor formations. Dr. Pico concludes that the extraordinary varieties of the symptoms produced may lead to confusion, also that the embryologic duality and histology of the adrenal may eventuate in multiple varieties of blastoma. The clinical polymorphism here is noteworthy, therefore, for purposes of orientation and in order to enable one to make a correct diagnosis methodic procedure is essential. This can be accomplished only by a thorough study of the symptomatology of the syndromes enumerated. The author intentionally omitted etiologic, physiopathologic and therapeutic consideration. His objective was to stress diagnosis. In other words, a guide for proper recognition of neoplasms of the adrenal is offered. It is a good book, and it welds an additional link in the chain of these often confusing clinical entities. It is written in Spanish.

Ophthalmology and Otolaryngology. Prepared and edited by the Subcommittees on Ophthalmology and Otolaryngology of the Committee on Surgery of the Division of Medical Sciences of the National Research Council. Ophthalmology: Prepared and edited by the Subcommittee on Ophthalmology. Harry S. Gradle, Chairman. Otolaryngology: Prepared and edited by the Subcommittee on Otolaryngology. Harris P. Mosher, Chairman. Volume II. Military Surgical Manuals. Cloth. Price, $4. Pp. 331, with 124 illustrations. Philadelphia & London: W. B. Saunders Company, 1942.

This military surgical manual is divided into two parts, ophthalmology and otolaryngology. It is written mainly for the surgeon and internist who may be called on in military practice to treat injuries and diseases of the eye, ear nose and throat and is not intended to be primarily a textbook for the specialist.

The section on ophthalmology consists of one hundred and fifty-seven pages and seventy-three illustrations written by seven contributors, each of national prominence. There are eight chapters, which include functional testing and examination of the eyes, injuries, local anesthesia about the orbit, medical treatment and surgical procedures. The text is well illustrated, clear, concise and to the point. The various necessary procedures are outlined step by step.

The section on otolaryngology consists of one hundred and forty-two pages and fifty-one illustrations. There are twelve chapters, contributed by sixteen authors, devoted to the various medical and surgical phases of the ear, nose and throat. Considerable space is devoted to primary treatment of gunshot wounds of the face, a topic of vital importance. As in the previous section, the text is brief and to the point. However, there could be more illustrations, which would be of inestimable value to the general practitioner.

The book as a whole is easily readable and is a definite improvement over the manual issued in 1917 during the first world war, which was much too brief. The new manual should be required reading for every doctor in the medical corps.

Essentials of Pathology. By Lawrence W. Smith, M.D., Professor of Pathology, Temple University School of Medicine, Philadelphia, and Edwin S. Gault, M.D., Associate Professor of Pathology, Temple University School of Medicine. With a foreword by James Ewing, M.D. Second edition. Fabrikoid. Price, $10. Pp. 904, with 679 illustrations, including 13 color plates. New York & London: D. Appleton-Century Company, Inc., 1942.

Concerning the former edition of "Essentials of Pathology," the authors state in the preface "The most universal criticism which was registered related to the brevity of the chapters devoted to the consideration of general pathology, the material being almost exclusively morphologic." This defect has been corrected by rewriting the first thirteen chapters with addition of approximately 30 per cent of new material. The remaining fifty-five chapters, the case histories and illustrations are practically unchanged. Fifteen pages of bibliography are included in this second edition. These references have been carefully chosen and appear to be quite adequate for the beginning student.

The main features distinguishing this textbook from others is the use of 295 carefully selected case histories with autopsy data to illustrate the dynamics of disease processes. In most instances photographs selected from presented cases are included. Approximately 25 per cent of the book is devoted to general pathology, 20 per cent to oncology and 55 per cent to systemic pathology.

The authors have done an excellent job in correlating embryology, physiology, biochemistry and bacteriology with the study of disease. Considerable attention is given to such topics as vitamin deficiency, virus infection, dental caries, arthritis, shock and other important conditions which are often minimized in textbooks of pathology. The section on parasitic diseases is excellent and quite comprehensive. This is particularly apt at the present time, when tropical medicine is becoming of increasing practical importance.

In general the material is fairly well balanced. There is some disproportion, however; e. g., twenty-one and one-half pages are devoted to diseases of the thyroid gland and less than one page to diseases of lymph nodes. Concerning lobar pneumonia, some might question the "lymphatic method of distribution" of organisms in view of the recent work of Robertson and his associates. The authors' description of the initial tuberculous lesion is not in accord with the general view. Obstructive nephropathy is given scant attention: no mention is made of tubular obstruction by precipitated sulfonamide compounds. It is unfortunate that a book such as this, which should be used a great deal, is too large to fit on a standard book shelf: it measures 11½ by 9¼ inches.

With some discount for case histories, the book contains approximately 10 per cent more words than the average of three leading textbooks of pathology, more than any one of them. This material is well indexed. It is profusely illustrated with excellent photographs and contains thirteen full page color plates. The colored reproductions of various blood elements are especially praiseworthy. In the opinion of the reviewer this is not only an excellent laboratory manual but a good general textbook which adequately presents the essentials of pathology.

Diseases of Metabolism: Detailed Methods of Diagnosis and Treatment. A Text for the Practitioner. Edited by Garfield G. Duncan, M.D., Chief of Medical Service "B," Pennsylvania Hospital, Philadelphia. Cloth. Price, $12. Pp. 985, with 158 illustrations. Philadelphia & London: W. B. Saunders Company, 1942.

This volume achieves its avowed purpose, as indicated by the title, to a commendable degree. It is partly because of the lack of such textbooks as this that the subject is often considered to be difficult by the average practitioner. However, difficult or not, our expanding knowledge of the subject has shown that it vitally concerns a large proportion of the patients who present themselves for treatment. It is therefore incumbent on all physicians to keep abreast of it. In accordance with the recent trend, fifteen different contributors, most of them noted for their achievements in their special fields of interest, have participated in this work. C. N. H. Long describes carbohydrate metabolism, Abraham White protein metabolism and lipid metabolism, Abraham Cantarow mineral metabolism, John P. Peters water balance in health and in disease, Leandro M. Tocantins the nutritional and metabolic aspects of disorders of the blood, Tom D. Spies and Hugh R.

Butt vitamins and avitaminoses, L. H. Newburgh undernutrition, Frank A. Evans obesity, Edward Mason xanthomatoses, glycogen disease and disturbances of intermediary metabolism, Walter Bauer and Friedrich Klemperer gout, Garfield G. Duncan hyperinsulinism, diabetes insipidus and diabetes mellitus, and Abraham Cantarow melituria.

As in all such assemblages, there is some unevenness in quality from chapter to chapter. But it is fair to say that the average is high. About two hundred pages are devoted to diabetes mellitus. The large chapter on vitamins and avitaminoses is very timely and ably done. The chapter on obesity is particularly good.

The Sulfonamide Compounds in the Treatment of Infections. By Maurice A. Schnitker, M.D., Attending Physician, Toledo Hospital, Toledo. Edited by Henry A. Christian, A.M., M.D., LL.D. [Reprinted from Oxford Loose-Leaf Medicine with the same Page Numbers as in that Work.] Cloth. Price, $2. Pp. 25-195. New York, Toronto & London: Oxford University Press, 1942.

This book, which is reprinted from Oxford Loose-Leaf Medicine with the same page numbers as in that work, represents an attempt to present a reasonably brief but also complete review of present knowledge of the sulfonamides. The contents include an introduction and discussions of the history, chemistry, assay and pharmacology of these compounds. Under separate chapters are presentations of the methods of administration and dosage, clinical uses, toxic effects and their treatment, of sulfanilamide, sulfapyridine, sulfathiazole, sulfadiazine and sulfaguanidine. Other chapters offer brief reviews on chemotherapeutic agents such as prontosil, neoprontosil, sulfanylsulfanilamide, sulfanyl-monomethyl-sulfanilamide, sulfanyl-dimethyl-sulfanilamide, benzyl-sulfanilamide, sulfa-methylthiazole, sulfacetamide and promin. A review is also included on the local use of the sulfonamide compounds as well as on their prophylactic use. As a source of information on the chemical and pharmacologic background, therapeutic efficacy and toxicity of the sulfonamides, this book is sufficiently complete and accurate to satisfy the harassed student, the busy practitioner and the hurrying lecturer. Obviously it cannot be expected to meet the needs of the researchist.

Atlas of Otolaryngic Pathology. Prepared at the Army Medical Museum, Office of the Surgeon General, U. S. Army, Largely from Material in the Registry of Otolaryngic Pathology. By J. E. Ash, Col., Medical Corps, U. S. Army, J. L. Bernier, Capt. D. C., and Roy M. Reeve. Third edition. Paper. Price, $5. Pp. 176, with illustrations. Omaha: American Academy of Ophthalmology and Otolaryngology, 1942.

Col. J. M. Ash, curator of the Army Medical Museum and its extensive registries of pathology, has now enlarged and elaborated the original photographic atlas of gross and microscopic pathology of the nose, throat and ear which was issued in 1939 and thereafter through the provision of funds by the American Academy of Ophthalmology and Otolaryngology. These excellent reproductions of typical photomicrographs, with accompanying text, have become an integral part of the prescribed "reading course" for residents in otolaryngology which has for several years been a valuable contribution by the academy to training in the specialty and in preparation for examination by the Board of Otolaryngology. Several new subjects have been covered in this edition, notably lesions of the jaws, mouth, external ear and nose. Colonel Ash and his staff deserve great credit for the completion of this highly technical task in the face of personnel and supply difficulties incidental to war conditions. Not a substitute for study of microscopic sections, this fine compilation is nevertheless of continuing value to the average practitioner of otolaryngology as well as to the beginner and the student.

War and the Doctor: Essays on the Immediate Treatment of War Wounds. Edited by J. M. Mackintosh, M.D., Chief Medical Officer of the Department of Health for Scotland. Cloth. Price, $2. Pp. 135. Baltimore: William Wood & Company, [1942].

The essays in this book are based on a series of lectures delivered to the Edinburgh Branch of the British Medical Association. They emphasize such aspects of war as the neuroses, shock and hemorrhage, wounds, first aid instruction and emergency surgery in the field. Each of the essays is written by an author who has had personal experience in the field concerned.

First Aid: Surgical and Medical. By Warren H. Cole, M.D., F.A.C.S., Professor and Head of the Department of Surgery, University of Illinois College of Medicine, Chicago, and Charles B. Puestow, B.S., M.S., M.D., Associate Professor of Surgery, University of Illinois College of Medicine. Fabrikoid. Price, $3. Pp. 351, with 92 illustrations by Carl Linden in collaboration with Tom Jones of the Illustration Studios of the University of Illinois College of Medicine. New York & London: D. Appleton-Century Company, Incorporated, 1942.

This volume is planned primarily for the medical student and practitioner who finds today that first aid is one of his greatest concerns. The book gives special consideration to emergencies related to the war, but it is realized that first aid is equally if not more important in civilian life and in industry. The volume is not the work of a single author; each of the chapters concerned is by a physician who has given special consideration to the problems. For example, injuries to the large blood vessels are discussed by de Takats, medical emergencies by Robert W. Keeton, gas and bomb raids by Major Harold C. Lueth, injuries of the scalp and skull by Eric Oldberg. The opening chapter on precautions and limitations in first aid work is obviously one of the most important and is accordingly emphasized by the type used. Throughout the book the discussions are practical, the illustrations carefully designed to supplement the text, the consideration succinct and well organized. The book can be highly recommended as a direct, authoritative presentation of a problem immediately important. No doubt much of the advice here contained is likely to be utilized in revisions of the Red Cross manual, which certainly at this time requires editing to bring it up to modern points of view.

Cabot and Adams Physical Diagnosis. Thirteenth edition. By F. Dennette Adams, M.D., Instructor in Medicine, Harvard Medical School Courses for Graduates, Boston. Cloth. Price, $5. Pp. 888, with 399 illustrations. Baltimore: William Wood & Company, 1942.

This represents a thorough revision of the previous edition, with many changes and new illustrations which serve to keep the textbook fresh and up to date. The book is comprehensive but maintains its convenient size by conciseness and terse, vivid descriptions amplified by illustrations. One of the peculiar features of the book, which has enabled it to maintain a position of leadership through thirteen editions and forty years, is the interesting manner in which it relates signs and symptoms to the various clinical entities. The salient features of the various syndromes and diseases are selected with obvious care and discrimination without in any way neglecting descriptions of signs and symptoms and the technic of eliciting them. This textbook is recommended not only for medical students but for those clinicians who wish to have a ready reference work at their disposal.

American Jewish Physicians of Note: Biographical Sketches. By Solomon R. Kagan, M.D. Cloth. Price, $5. Pp. 304, with 129 illustrations. Boston: Boston Medical Publishing Company, 1942.

This volume is intended to supplement previous editions which present biographic sketches of Jewish physicians, including those who have attained eminence as investigators, teachers or leaders. The volume makes no pretense at completeness but is exceedingly useful for the material that it offers. The sketches seem to have been arranged in the book largely at random. The book includes also a chronology of important discoveries.

Visual Aids in Safety Education: Supplement 1. Prepared by the Safety Education Projects of the Research Division. Paper. Price, 25 cents. Pp. 59. Washington, D. C.: National Education Association of the United States, 1942.

The Safety Education Projects of the Research Division of the National Education Association has prepared this supplement to a previous publication with the same name published two years ago. All films have been previewed by members of the committee with special attention to objectionable advertising, failure to observe modern teaching methods, inexperienced acting and outmoded clothes and automobiles. Two hundred and ninety-nine motion pictures, sound-slide films and film strips are listed, covering all phases of safety education. The old style lantern slide has almost ceased to exist, for only four subjects are mentioned using this method of presentation. The pamphlet also contains the names of 362 distributors of safety films and slides and 61 distributors of safety posters. It should prove useful to persons interested in safety education.

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Queries and Minor Notes

THE ANSWERS HERE PUBLISHED HAVE BEEN PREPARED BY COMPETENT AUTHORITIES. THEY DO NOT, HOWEVER, REPRESENT THE OPINIONS OF ANY OFFICIAL BODIES UNLESS SPECIFICALLY STATED IN THE REPLY. ANONYMOUS COMMUNICATIONS AND QUERIES ON POSTAL CARDS WILL NOT BE NOTICED. EVERY LETTER MUST CONTAIN THE WRITER'S NAME AND ADDRESS, BUT THESE WILL BE OMITTED ON REQUEST.

INTRACRANIAL HEMORRHAGE OF NEWBORN

To the Editor:—What is the current status of handling intracranial hemorrhage of the newborn, any type, early or the type that shows itself twenty-four or seventy-two hours after birth? I am particularly interested in spinal puncture; is it used at all, or is it done repeatedly? Are there any advocates of intravenous hypertonic solutions? In your answer, please disregard reference to vitamin K and other preventive measures.

William H. Dixon, M.D., Rocky Mount, N. C.

ANSWER.—The managment of intracranial hemorrhage of the newborn should consist in keeping the infant as quiet as possible; consequently, energetic treatment should be avoided. The head of the crib should be elevated to reduce cerebral venous pressure. Phenobarital in small doses may be administered for relief of convulsions or extreme restlessness.

There is a great difference of opinion about the value of lumbar puncture in these cases. If the fontanel is bulging and a pronounced increase of intracranial pressure is suspected, lumbar puncture will probably be made, though when the hemorrhage has been diffuse and oozing continues the withdrawal of fluid gives only temporary relief. If subdural bleeding can be recognized, a puncture may be made at the lateral angle of the fontanel.

In the literature there are a number of references to surgical intervention. Most neurosurgeons show considerable skepticism about operation. In newborn and young infants the hazard of brain operation is serious; most of the patients succumb to shock. The number of successful results is small. Certainly infratentorial hemorrhages are not amenable to operative treatment. Even when the hemorrhage is supratentorial, operation should not be undertaken lightly.

It is not usually considered advisable to operate until the third or fourth day after birth. Even if the blood clots are removed it is still doubtful if complete recovery will ensue because of the damage which already has been done to the underlying brain tissue. Moncrieff (Alan: *Brit. M. J.* **1**: 1068 [June 16] 1934) recommended the infusion of hypertonic dextrose solutions in cases of commotio cerebri. The same author also recommends that enemas of 60 or 90 cm. of 10 per cent salt solution should be given every four hours in the hope that brain pressure may be relieved.

CAPILLARY FRAGILITY AND HEMORRHAGE DURING MENSTRUATION

To the Editor:—A few of our local dentists will not extract a tooth from a menstruating woman because postoperative hemorrhages occur with greater frequency in these cases than otherwise as the result of changes in the blood chemistry at this time. Is there a scientific basis for such a statement or is it merely a coincidence?. Any information will be appreciated.

M.D., Pennsylvania.

ANSWER.—There is some scientific basis for this clinical observation. Brewer (J. I.: *Am. J. Obst. & Gynec.* **36**: 597 [Oct.] 1938) found that in women with normal ovulatory menstruation there are rhythmic changes in the skin capillaries associated with the cyclic menstrual rhythm. These changes are essentially in capillary fragility. During the few days prior to and on the first day of menstruation, capillary hemorrhage is produced with relatively greater ease than during the remainder of the cycle. These rhythmic changes are the direct result of vascular spasm. In functional uterine bleeding, the vascular rhythm in the skin capillaries is profoundly disturbed and is completely dissociated from the menstrual rhythm. These facts indicate that menstruation which is evidenced as a local vascular phenomenon is a part of a demonstrable generalized vascular phenomenon present in the entire body.

Increased capillary permeability can be demonstrated by the Rumpel-Leede test, which is performed by applying a moderately tight rubber bandage around the upper arm for ten minutes. When it is positive, subcutaneous hemorrhages appear below the bandage. In normal women such petechial spots are readily produced at the time of the menses but rarely in the preovulatory phase.

LOCAL ANESTHESIA AND INTERCOSTAL BLOCK FOR ABDOMINAL WALL

To the Editor:—Ogilvie (Surg., Gynec. & Obst. **68**: 295 (Feb. 15) 1939) advises the use of a solution for local anesthesia of the abdominal wall which is composed of procaine hydrochloride 0.5 per cent and quinine and urea hydrochloride 0.25 per cent. What are the advantages and disadvantages of the addition of the quinine and urea hydrochloride to a local anesthetic solution? Ogilvie advocates a technic of abdominal wall block by infiltration of the lateral borders of the rectus sheath. In the same journal (**71**: 194 [Aug.] 1940) Bartlett advocates intercostal nerve block beneath the lower six ribs in the midaxillary line bilaterally for anesthesia of the abdominal wall above a level 2 inches below the umbilicus. What are the relative advantages and disadvantages of these two methods of anesthesia of the upper abdominal wall?

M.D., Alaska.

ANSWER.—The advantage of adding quinine and urea hydrochloride to a local anesthetic solution is that it prolongs the local anesthesia considerably. The disadvantage is that not all persons tolerate the drug, and, in some instances in which it has been used stronger than 0.25 per cent, sloughing has occurred. The advantage of abdominal wall block at the border of the rectus sheath is that anesthesia lasts longer than when intercostal block is done and there is less bleeding when the incision is made. Less general anesthesia is required for the intra-abdominal part of the operation in most cases than if local anesthesia is not used. The advantage of intercostal block advocated by Bartlett is that, in those patients who have abdominal scars and the bowel is adherent to the abdominal wall, the abdominal wall block is to be avoided for fear that the bowel might be perforated by the needle in doing the block. The intercostal block produces anesthesia and relaxation of the abdominal wall without injecting into the abdominal wall itself. For the patient who is debilitated so that one must restrict the amount of local anesthetic to be used, intercostal block permits more anesthesia with less solution than does abdominal wall block.

INDUSTRIAL POISONING ASSOCIATED WITH DROSSES

To the Editor:—I have been observing two men for the past month who work together in a plant that has to do with reclaiming drosses. Both men have mild symptoms of multiple transient joint pains and neuritic pains. Recently they have been complaining of a bad taste in the mouth, and bleeding of gums when brushing their teeth, mild general malaise and slight anorexia; all symptoms are moderate and at present more annoying than anything else. Examination is entirely negative except for a slight drop in hemoglobin and red cell count. The metals and gases that they come in contact with are tellurium, chlorine, sulfur and antimony; for the most part they use protection whenever they think it advisable. If you have any information on these metals and gases I would appreciate your sending it to me or telling me where I might be able to read up on them.

R. D. Campbell, M.D., Cleveland.

ANSWER.—Drosses, skimmings and slags resulting from molten metal operations sometimes provide highly difficult problems in industrial toxicology. Most metals are impure, and the quantity of impurities often is appreciable even in drosses. Lead, arsenic and zinc are common impurities for many metals. In a metal dross recovery plant the type and quantity of impurities may vary almost daily. Only the unwary would commit himself to any specific exposure in general metal dross recovery work. Granting that some injury of occupational disease nature may arise under such circumstances as described, it is appropriate to contemplate mixed or combined causes. This is no new concept of occupational disease etiology, having been sponsored years ago by Hayhurst and other physicians. Naturally any disease state from mixed causes may present such bizarre manifestations as to defy classification. The symptoms mentioned suggest antimony poisoning, but there have been few cases of reported antimony poisoning in this country to furnish the manifestations of the antimony syndrome. For practical purposes this dross recovery work should be well ventilated to the end that all gases and fumes shall be discharged to harmless points. The intermittent, haphazard wearing of respirators is not sufficient. Should the severity of the infirmities of these workers increase, appropriate laboratory examination of urine, feces and blood should be made for specific materials such as lead, arsenic, antimony, tellurium and selenium. In antimony poisoning a high eosinophilia is believed to occur. In lead poisoning repeated quantitative lead in urine determinations should be made. On the assumption that antimony might be the chief offender, a number of references are given:

Johnstone, R. T.: Occupational Diseases, Philadelphia and London, W. B. Saunders Company, 1941.

Bradley, W. R., and Frederick, W. G.: The Toxicity of Antimony: Animal Studies, *Indust. Med.*, Industrial Hygiene Section **2**: 15 (April) 1941.

Oliver, Thomas: Health of Antimony Oxide Workers, *Brit. M. J.* **1**: 1094 (June 24) 1933.

Antimony Poisoning Due to the Use of Enameled Vessels, Ministry of Health, Memo. 171, Med., H. M. Stationery Office, 1933, in *Bull. Hyg.* **8**: 445 (June) 1933.

Occupational Disease Occurring in a Buffer Working on Britannia Metal, *U. S. Month. Labor Rev.* **22**: 184 (Jan.) 1926.

UNUSUAL LARYNGITIS AND CHONDRITIS

To the Editor:—Eighteen months ago a woman aged 27 had an acute infection of the left side of the larynx. This began as a small ulcer and then rapidly became a widespread necrosis. The Wassermann reaction was negative; bacteriologic studies showed a number of organisms, mainly streptococci of nonhemolytic variety and many Vincent's organisms, both spirochetes and bacilli. It involved the posterior region, including the interarytenoid region. Healing was rapid with neoarsphenamine, sodium perborate and powdered methylene blue, but every few months there would be a recurrence with great suddenness—so suddenly that the last time I looked at her larynx in the morning there were no symptoms and yet that night there was a full blown ulceration with edema, final discharge and what looked to me to be at least a partial separation of the processus vocalis. The best description I can give is that it reminded me of cancrum oris on a mild and localized scale. The fear that another upset would permanently injure her voice led me to ask a competent radiologist if irradiation would help. He gave five daily treatments, the various factors of which I do not know. It healed well and has not recurred in a year's time; however, about a month later both cords got hyperemic, and, while this condition has lessened, the attached margins have a dusky cyanotic redness. The destruction has been repaired with the possible exception that the transverse arytenoid muscle does not quite fully approximate the posterior ends of the cords. The patient can talk, although in a few moments her voice plays out. Is there anything that can be done for the radiation erythema? I am sure this is due to the radiation, for the right cord never was involved in the process of infection and is less inflamed than the other cord, which was nearer the tube.

M.D., Arkansas.

ANSWER.—While the cause of the original infection is not known, the subsequent changes were due to a chondritis of the arytenoid cartilage with probably some involvement of the signet of the cricoid. The frequent recurrences with edema and purulent discharge suggest that small sequestrums of cartilage were discharged at irregular intervals. Irradiation probably aided in securing more prompt resolution.

Five roentgen treatments should not produce a severe erythema unless the dosage was larger than commonly employed. It would seem that the persistence of a low grade infection would be a likely explanation in spite of the fact that there has been no recurrence of severe symptoms for about one year. If it is due to irradiation there is relatively little to be done, although some patients secure relief by the employment of a bland medicated oil, preferably mentholated, a vegetable oil base being used, which may be instilled into the larynx or introduced with an atomizer. The patient can be instructed to use this and can employ it several times daily.

BULLET WOUNDS OF PULMONARY VESSELS AND SPEED OF DEATH

To the Editor:—I should like some information as to the occurrence of death from gunshot wounds. A man was shot laterally through the chest from right to left by a 0.25-35 caliber bullet fired from a distance of 12 inches. The bullet passed through a window of a car with shatter proof glass and then passed through the body of the man. In the course through the body the bullet completely severed the pulmonary artery just above the heart. The coroner's jury asked me how long the man lived after such a wound. Basing my answer on an electrocardiogram taken a year or two ago in a prison when a man was executed by a firing squad, I answered that he probably lived about fifteen seconds. They also asked me if, after the bullet passed through his body, he would have been able to shut off the switch of his motor or to have opened the car door. My answer was that he could do neither of these. I would also be interested to know whether or not the mechanical force of a bullet this size would have been sufficient to push the man over. Evidence would seem to indicate that, at the time the man was shot, the car door on his left was open and that the body fell out of the car. He was lying at right angles to the car with his feet near the running board and his head away from it. The body was streched out, lying on its back. Would there have been enough muscular reaction for the body to get in this position or would the supposition be that, if it was in this position, it would have had to be placed there by some one else? This shooting occurred as a hunting accident—it is not a medicolegal case. If consistent, I should be pleased to have as much information on these matters as possible.

M. A. Shillington, M.D., Glendive, Mont.

ANSWER.—Bullet wounds of the aorta and pulmonary artery as a general rule are quickly fatal. This is true also of perforations of the innominate artery and the iliac vessels and to a lesser extent of the subclavian and carotid arteries. Gunshot wounds of the cardiac auricles are more rapidly fatal than those of the ventricles, especially the left ventricle, because the thick muscular wall may check bleeding by its contraction.

If no communication exists between the pericardium and the pleura, death may occur rapidly by asphyxia from compression of the heart. However, if the blood has an opportunity to leak into one or both pleural cavities, the death may be delayed for several minutes.

Bullet injuries of these structures are not instantly fatal. Victims may live for several minutes; in fact it is recorded that some have walked or run considerable distances and even climbed stairs. Under these circumstances caution must be exercised in expressing an opinion whether a person shot through the pulmonary artery could or could not turn off the ignition or open the door of a car before collapsing.

Ordinarily the sequence of the rapidity of a fatal issue following gunshot wounds is as follows: the aorta, main pulmonary artery and cardiac auricles; the ventricles; the iliacs and innominate artery; the femorals, subclavians and carotid arteries.

In wounds through the large veins, namely the cavae, iliacs and so on, the time interval between the receipt of the injury and death may be longer, in comparison to wounds of the corresponding arteries. Each case must be judged individually.

HORNER'S SYNDROME

To the Editor:—Are there two kinds of Horner's syndromes: (1) paralytic, with miosis, enophthalmos, ptosis and anhidrosis and (2) irritative, with mydriasis, exophthalmos and the like? I would appreciate it if you would list references with the reply. Archie Sheinmel, M.D., Alexandria, La.

ANSWER.—Horner's syndrome or Horner-Bernard syndrome is characterized by miosis, decreased palpebral aperture (pseudoptosis), retraction of the eyeball (enophthalmos), dilatation of the blood vessels, anhidrosis and finally increase of temperature on the face and head. All these symptoms occur on the same side as the lesion. This syndrome was described by Claude Bernard as well as by Horner. Bernard sectioned the sympathetic nerve in the neck and observed the signs mentioned. There is only one kind of Horner's syndrome. That is due to a lesion of the cervical sympathetic resulting in paralysis. Symptoms of irritation of the cervical sympathetic usually precede or occur simultaneously with paralysis. Dorland's Medical Dictionary of 1929, Tilney and Riley second edition, page 356, Wechsler, fourth edition, page 70, Church and Peterson, 1909, page 107, Bing and Haymaker, fifth edition, page 267, Oppenheim, 1911, volume 2, page 1315, Purves-Stewart, eighth edition, page 568, Brock, 1937, page 67, Dana, 1915, page 102, and four other textbooks on neurology all agree with the opening statement given.

NERVE SUPPLY OF CERVIX UTERI

To the Editor:—Is there any adequate discussion of the nerve innervation of the cervix uteri? In addition, I should like a picture or diagram of the nerves if either is available. Harry Anker, M.D., Akron, Ohio.

ANSWER.—The nerve supply of the uterus comes from both the sympathetic and the cerebrospinal system. The motor fibers are derived from the sympathetic system passing down from the aortic plexus. They are reinforced by fibers from the solar, renal and genital ganglions, forming a large plexus above the promontory of the sacrum near the bifurcation of the aorta, called the great uterine plexus. From here the fibers pass on either side of the rectum through the hypogastric plexuses to the sides of the uterus but mainly to the great cervical ganglion and thus into the uterus. Cerebrospinal fibers come from the pneumogastric, phrenic and splanchnic nerves and follow the same course. The uterus also receives innervation from the lumbosacral autonomic system by way of the pelvic nerve (second, third and fourth sacrals) to the uterocervical ganglions.

Sensory fibers come from the spinal cord through the sacral nerve, being also distributed by way of the great cervical ganglion. The latter, or Frankenhäuser, ganglion is a triangular mass of ganglion cells and nerve fibers lying behind and at the side of the cervix and upper vagina.

There is an explanatory diagram in De Lee's Principles and Practice of Obstetrics, seventh edition, Philadelphia, W. B. Saunders Company, 1938, page 81.

COLOR BLINDNESS

To the Editor:—A soldier aged 22 has lost a number of chances for advancement because of color blindness. Believing color blindness to be congenital, I had informed him that there was no treatment for it. He has worked around moving picture projectors and photostatic equipment and believes this work may have had something to do with his condition. He states that some of his comrades with a similar condition have been given treatment by army doctors. He matches yarns correctly but sees the wrong numbers on color plates unless the plate is in a strong natural light and the pages are turned slowly. Is there any known correction for this condition? M.D., New Mexico.

ANSWER.—Color blindness is a congenital defect and in the true sense of the term is never acquired. Extraneous conditions, such as those mentioned, have no influence on the color perception, which may vary from complete absence of color recognition to mere inability to differentiate various shades. There is no known correction for this condition despite the claims of some optometrists.

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